# LINCOMYCIN DERIVATIVES POSSESSING ANTIBACTERIAL ACTIVITY

## CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. Patent Application No. 10/642,807, filed August 15, 2003, which claims the benefit under 35 U.S.C. §119(e) of U.S. Provisional Application No. 60/403,770 filed on August 15, 2002, the disclosures of which are hereby incorporated by reference.

## BACKGROUND OF THE INVENTION

### FIELD OF THE INVENTION

[0002] This invention relates to lincomycin derivatives that exhibit antibacterial activity.

### STATE OF THE ART

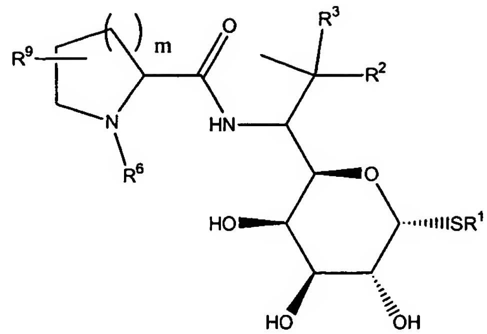
[0003] Lincomycin is a biosynthetic product that adversely affects growth of various microorganisms, in particular gram positive bacteria. The characteristics and preparation of lincomycin are disclosed in U.S. Patent 3,086,912. A variety of derivatives of lincomycin, which also have antimicrobial activity, have been prepared. These derivatives include, for example, clindamycin, which is described in U.S. Patent 3,496,163.

[0004] Lincomycin derivatives remain attractive targets for antibacterial drug discovery. Accordingly, lincomycin derivatives that possess antimicrobial activity are desired as potential antibacterial agents.

## SUMMARY OF THE INVENTION

[0005] The present invention provides lincomycin derivatives that possess antibacterial activity.

[0006] In one of its composition aspects, this invention is directed to a compound of formula (I):



(I)

wherein:

$R^1$ is alkyl;

$R^2$ and $R^3$ are independently H, alkyl, hydroxy, fluoro, or cyanoalkyl or one of $R^2$ and $R^3$ is $=NOR^7$ and the other is absent, or one of $R^2$ and $R^3$ is $=CH_2$ and the other is absent, with the provisos that both $R^2$ and $R^3$ are not H; when one of $R^2$ and $R^3$ is fluoro, the other is not hydrogen or hydroxy; and when one of $R^2$ and $R^3$ is hydroxy, the other is not fluoro, hydrogen, or hydroxy;

$R^6$ is selected from the group consisting of H, alkyl, hydroxyalkyl, -C(O)O-alkylene-cycloalkyl, -C(O)O-alkylene-substituted cycloalkyl, -C(O)O-alkyl, -C(O)O-substituted alkyl, -C(O)O-aryl, -C(O)O-substituted aryl, -C(O)O-heteroaryl, -C(O)O-substituted heteroaryl, $-[C(O)O]_p$-alkylene-heterocycle, $-[C(O)O]_p$-alkylene-substituted heterocycle, wherein p is 0 or 1;

$R^7$ is H or alkyl;

$R^9$, which can be singly or multiply substituted in the ring on the same or different carbons, is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkoxyalkoxy, cycloalkyl, substituted cycloalkyl, substituted oxygen, substituted nitrogen, halogen, phenyl, substituted phenyl, $-(CH_2)_n-OH$, $-(CH_2)_n-NR^4R^5$, -alkylene-$R^a$ where $R^a$ is selected from monofluorophenyl and monochlorophenyl, and branched chain isomers thereof wherein n is an integer of from 1 to 8 inclusive and $R^4$ and $R^5$ are H or alkyl; and

m is 0, 1, 2 or 3; and

prodrugs, tautomers or pharmaceutically acceptable salts thereof;

with the proviso that the compound of formula I has a minimum inhibition concentration of 32 $\mu$g/mL or less against at least one of the organisms selected from the group consisting of Streptococcus pneumoniae, Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus

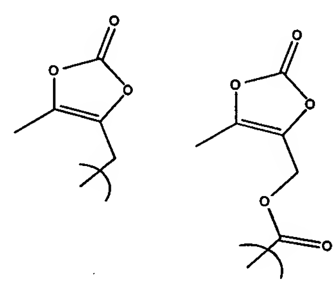
faecalis, Enterococcus faecium, Haemophilus influenzae, Moraxella catarrhalis, Escherichia coli, Bacteroides fragilis, Bacteroides thetaiotaomicron, and Clostridium difficile.

**[0007]** In one embodiment, m is 0. In another embodiment, m is 1. In another embodiment, m is 2. In another embodiment, m is 3.

**[0008]** In a preferred embodiment, $R^1$ is methyl.

**[0009]** In one embodiment, one of $R^2$ and $R^3$ is H, and the other is alkyl. In one embodiment, one of $R^2$ and $R^3$ is H, and the other is methyl. In one embodiment, one of $R^2$ and $R^3$ is H, and the other is cyanoalkyl. In one embodiment, both of $R^2$ and $R^3$ are F. In one embodiment, one of $R^2$ and $R^3$ is hydroxy, and the other is alkyl. In one embodiment, $R^2$ and $R^3$ together are hydroxyimino or alkoxyimino. In one embodiment, $R^2$ and $R^3$ together are methylene (=$CH_2$).

In a preferred embodiment, $R^6$ is H, alkyl, or hydroxyalkyl. In a preferred embodiment, $R^6$ is selected from the group consisting of H, methyl, ethyl, 2-hydroxyethyl, 2-methyl-2-hydroxyethyl, and 3-hydroxypropyl. In another embodiment, $R^6$ is not one of the following:



**[0010]** In one embodiment, each $R^9$ is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxyalkoxy, cycloalkyl, cycloalkylalkyl, substituted cycloalkyl, substituted oxygen, substituted nitrogen, halogen, phenyl, substituted phenyl, -$(CH_2)_n$-OH, -$(CH_2)_n$-$NR^4R^5$, -alkylene-$R^a$ where $R^a$ is selected from monofluorophenyl and monochlorophenyl, and branched chain isomers thereof wherein n is an integer of from 1 to 8 inclusive and $R^4$ and $R^5$ are H or alkyl.

**[0011]** In one embodiment, $R^9$ is a substituted alkyl, and wherein the one or more substituents on the alkyl group are selected from the group consisting of halogen, oxygen, hydroxy, amine (primary), amine (secondary-amine substituted by alkyl above), amine (tertiary-amine substituted by alkyl as above), sulfur, -SH, and phenyl.

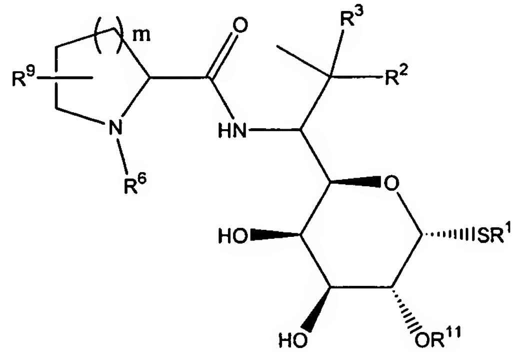
[0012] In a preferred embodiment, each $R^9$ is independently selected from the group consisting of halogen, alkyl, substituted alkyl, alkoxy, alkoxyalkoxy, substituted alkoxy, and cycloalkyl. In another preferred embodiment, each $R^9$ is independently selected from the group consisting of H, alkyl, and substituted alkyl.

[0013] In one embodiment, $R^9$ is selected from the group consisting of 1-ethylpropyl; 2-(4-fluorophenyl)ethyl; 2,2-difluoroethoxymethyl/fluoro; 2,2-difluoropentyl; 2-cyclobutyl-ethyl; 2-cyclopropyl-ethyl; 2-fluoroethoxy; 2-methoxyethoxy; 2-propoxy-ethyl; 3-(2-fluoro-ethoxy)-propyl; 3-(3-fluoro-propoxy)-propyl; 3-(4-chlorophenyl)propyl; 3-(cyclopropyl-methoxy)-propyl; 3,3,3-trifluoropropoxy; 3,3-difluorobutyl; 3,3-difluoropentyl; 3,3-difluoropropyl; 3,3-difluoropropyl/fluoro; 3-cyclobutyl-propyl; 3-cyclopentyl-propyl; 3-cyclopropyl-propyl; 3-ethoxy-propyl; 3-fluoropropoxy; 3-fluoro-propoxy-methyl; 3-fluoropropyl; 3-fluoropropyl/fluoro; 3-hydroxy-3-ethylpentyl; 3-methoxy-propyl; 3-propoxy-propyl; 4,4-difluorobutyl; 4,4-difluoropentyl; 4-fluorobutoxy; 4-fluorobutyl; 4-methoxy-butyl; 5,5-difluoropentyl; 5-fluoropentyl; butoxy; butyl; cyclobutyl-methyl; cyclohexyl; cyclohexyl-methyl; cyclopropyl-methoxy; cyclopropyl-methyl; ethyl; ethyl/fluoro; fluoro/butyl; fluoro/propyl; isobutyl; isopentyl; iso-propyl; methoxy; n-butyl; n-pentyl; pentoxy; pentyl; propoxy-methyl; and propyl. In another embodiment, $R^9$ is propyl.

[0014] In one embodiment, $R^9$ is selected from the group consisting of 1-ethylpropyl; 2-(4-fluorophenyl)ethyl; 2,2-difluoropentyl; 2-cyclobutyl-ethyl; 2-cyclopropyl-ethyl; 2-methoxyethoxy; 3-(2-fluoro-ethoxy)-propyl; 3-(4-chlorophenyl)propyl; 3,3-difluorobutyl; 3,3-difluoropentyl; 3,3-difluoropropyl; 3-cyclobutyl-propyl; 3-cyclopentyl-propyl; 3-cyclopropyl-propyl; 3-ethoxy-propyl; 3-fluoropropyl; 3-hydroxy-3-ethylpentyl; 3-methoxy-propyl; 3-propoxy-propyl; 4,4-difluorobutyl; 4-fluorobutyl; 5,5-difluoropentyl; 5-fluoropentyl; butoxy; butyl; cyclobutyl-methyl; cyclohexyl; cyclohexyl-methyl; cyclopropyl-methoxy; cyclopropyl-methyl; ethyl; isobutyl; isopentyl; iso-propyl; methoxy; n-butyl; n-pentyl; pentoxy; pentyl; propoxy-methyl; and propyl.

[0015] In one embodiment, $R^9$ not 2,2-difluoroethoxymethyl/fluoro; 2-fluoroethoxy; 2-propoxy-ethyl; 3-(3-fluoro-propoxy)-propyl; 3-(cyclopropyl-methoxy)-propyl; 3,3,3-trifluoropropoxy; 3,3-difluoropropyl/fluoro; 3-fluoropropoxy; 3-fluoro-propoxy-methyl; 3-fluoropropyl/fluoro; 4,4-difluoropentyl; 4-fluorobutoxy; 4-methoxy-butyl; ethyl/fluoro; fluoro/butyl; or fluoro/propyl.

**[0016]** In one of its composition aspects, this invention is directed to a prodrug compound of the formula (IV):



wherein $R^1$, $R^2$, $R^3$, and $R^9$ are as defined for formula I; wherein $R^6$ is as defined for formula I or is a suitable prodrug group which is cleavable *in vivo*; and wherein $R^{11}$ is H or a suitable prodrug group which is cleavable *in vivo*.

**[0017]** In one embodiment, the compound is a prodrug wherein $R^6$ is selected from the group consisting of hydrogen; 1-(acetyloxy)-ethyl-oxycarbonyl; 1-amino-2-methyl-butyl-carbonyl; 1-amino-2-methyl-butyl-carbonyl-oxy-methyl-oxycarbonyl; 1-amino-2-methyl-propyl-carbonyl; 1-amino-2-phenyl-ethyl-carbonyl; 1-amino-ethyl-carbonyl; 1-methyl-1,2,3,6 tetrahydro-pyridin-4-yl-oxycarbonyl; 1-methyl-1,4 dihydro-pyridin-3-yl-carbonyl; 1-methyl-3-oxo-but-1-enyl; 5-methyl-[1,3]dioxol-2-one-4-yl-methoxy-carbonyl; 5-methyl-[1,3]dioxol-2-one-4-yl-methyl; ethoxy-carbonyl; ethyl-carbonylamino-methyl; fluorenyl-methylene-oxy-carbonyl; phenoxy-carbonyl; piperidin-4-yl-carbonyl-oxy-methyl-oxycarbonyl; and pyridine-3-yl-carbonylamino-methyl.

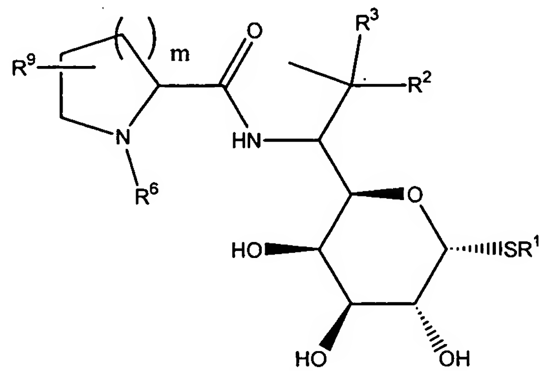
**[0018]** In another embodiment, the compound is a prodrug wherein $R^6$ is selected from the group consisting of hydrogen; 1-(acetyloxy)-ethyl-oxycarbonyl; 1-amino-2-methyl-butyl-carbonyl; 1-amino-2-methyl-butyl-carbonyl-oxy-methyl-oxycarbonyl; 1-amino-2-methyl-propyl-carbonyl; 1-amino-2-phenyl-ethyl-carbonyl; 1-amino-ethyl-carbonyl; 1-methyl-1,2,3,6 tetrahydro-pyridin-4-yl-oxycarbonyl; 1-methyl-1,4 dihydro-pyridin-3-yl-carbonyl; 1-methyl-3-oxo-but-1-enyl; ethyl-carbonylamino-methyl; piperidin-4-yl-carbonyl-oxy-methyl-oxycarbonyl; and pyridine-3-yl-carbonylamino-methyl.

**[0019]** In another embodiment, the compound is a prodrug wherein $R^6$ is not 5-methyl-[1,3]dioxol-2-one-4-yl-methoxy-carbonyl; 5-methyl-[1,3]dioxol-2-one-4-yl-methyl; ethoxy-carbonyl; fluorenyl-methylene-oxy-carbonyl; or phenoxy-carbonyl.

**[0020]** In another embodiment, the compound is a prodrug wherein $R^6$ is not 5-methyl-[1,3]dioxol-2-one-4-yl-methoxy-carbonyl; or 5-methyl-[1,3]dioxol-2-one-4-yl-methyl.

[0021] In a preferred embodiment, the compound is a prodrug wherein $R^{11}$ is selected from the group consisting of hydrogen; 2-(*N*-(2-morpholin-4-yl-ethyl)-amino-carbonyl)-ethyl-carbonyl; $-C(O)CH_2CH_2COOH$; *N,N*-dimethyl-amino-methyl-carbonyl; pentadecyl-carbonyloxy; and $-PO_3H_2$.

[0022] In a preferred embodiment, this invention provides compounds of formula (II)




(II)

wherein:

$R^1$ is alkyl;

$R^2$ and $R^3$ are independently H, alkyl, or cyanoalkyl, with the proviso that both $R^2$ and $R^3$ are not H;

$R^6$ is H, alkyl, or hydroxyalkyl;

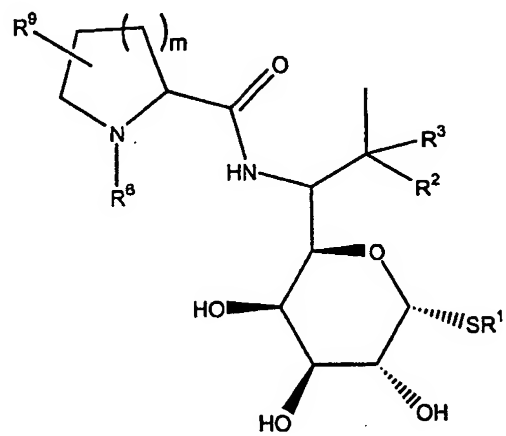
$R^9$, which can be singly or multiply substituted in the ring on the same or different carbons, is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxyalkoxy, cycloalkyl, substituted cycloalkyl, substituted oxygen, substituted nitrogen, halogen, phenyl, substituted phenyl, $-(CH_2)_n-OH$, $-(CH_2)_n-NR^4R^5$, -alkylene-$R^a$ where $R^a$ is selected from monofluorophenyl and monochlorophenyl, and branched chain isomers thereof wherein n is an integer of from 1 to 8 inclusive and $R^4$ and $R^5$ are H or alkyl; and

m is 1 or 2; and

prodrugs and pharmaceutically acceptable salts thereof;

with the proviso that the compound of formula II has a minimum inhibition concentration of 32 $\mu$g/mL or less against at least one of the organisms selected from the group consisting of Streptococcus pneumoniae, Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis, Enterococcus faecium, Haemophilus influenzae, Moraxella catarrhalis, Escherichia coli, Bacteroides fragilis, Bacteroides thetaiotaomicron, and Clostridium difficile.

[0023] In a particularly preferred embodiment, this invention provides compounds of formula (III):



(III)

wherein:

$R^1$ is alkyl;

$R^2$ and $R^3$ are fluoro;

$R^6$ is H, alkyl, or hydroxyalkyl;

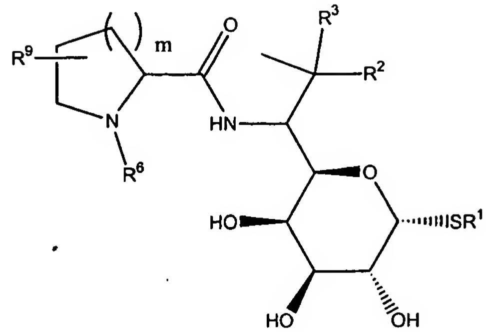
$R^9$, which can be singly or multiply substituted in the ring on the same or different carbons, is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxyalkoxy, cycloalkyl, substituted cycloalkyl, substituted oxygen, substituted nitrogen, halogen, phenyl, substituted phenyl, $-(CH_2)_n$-OH, -$(CH_2)_n$-$NR^4R^5$, -alkylene-$R^a$ where $R^a$ is selected from monofluorophenyl and monochlorophenyl, and branched chain isomers thereof wherein n is an integer of from 1 to 8 inclusive and $R^4$ and $R^5$ are H or alkyl; and

m is 1 or 2; and

prodrugs and pharmaceutically acceptable salts thereof,

with the proviso that the compound of formula III has a minimum inhibition concentration of 32 $\mu$g/mL or less against at least one of the organisms selected from the group consisting of Streptococcus pneumoniae, Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis, Enterococcus faecium, Haemophilus influenzae, Moraxella catarrhalis, Escherichia coli, Bacteroides fragilis, Bacteroides thetaiotaomicron, and Clostridium difficile.

In another preferred embodiment, this invention is directed to a compound of formula (IV):



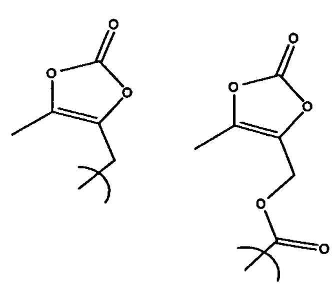
(IV)

wherein:

$R^1$ is alkyl;

$R^2$ and $R^3$ are independently H, or alkyl, hydroxy, fluoro, or cyanoalkyl or one of $R^2$ and $R^3$ is $=NOR^7$ and the other is absent, or one of $R^2$ and $R^3$ is $=CH_2$ and the other is absent, with the provisos that both $R^2$ and $R^3$ are not H; when one of $R^2$ and $R^3$ is fluoro, the other is not hydrogen or hydroxy; and when one of $R^2$ and $R^3$ is hydroxy, the other is not fluoro, hydrogen, or hydroxy;

$R^6$ is selected from the group consisting of -C(O)O-alkylene-cycloalkyl, -C(O)O-alkylene-substituted cycloalkyl, -C(O)O-alkyl, -C(O)O-substituted alkyl, -C(O)O-aryl, -C(O)O-substituted aryl, -C(O)O-heteroaryl, -C(O)O-substituted heteroaryl, -$[C(O)O]_p$-alkylene-heterocycle, -$[C(O)O]_p$-alkylene-substituted heterocycle, wherein p is 0 or 1 with the proviso that -C(O)O-substituted alkyl does not include the following:



$R^7$ is H or alkyl;

$R^9$, which can be singly or multiply substituted in the ring on the same or different carbons, is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxyalkoxy, cycloalkyl, substituted cycloalkyl, substituted oxygen, substituted nitrogen, halogen, phenyl, substituted phenyl, $-(CH_2)_n-OH$, -

$(CH_2)_n$-$NR^4R^5$, -alkylene-$R^a$ where $R^a$ is selected from monofluorophenyl and monochlorophenyl, and branched chain isomers thereof wherein n is an integer of from 1 to 8 inclusive and $R^4$ and $R^5$ are H or alkyl; and

m is 1 or 2; and

prodrugs, tautomers or pharmaceutically acceptable salts thereof;

with the proviso that the compound of formula I has a minimum inhibition concentration of 32 $\mu$g/mL or less against at least one of the organisms selected from the group consisting of Streptococcus pneumoniae, Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis, Enterococcus faecium, Haemophilus influenzae, Moraxella catarrhalis, Escherichia coli, Bacteroides fragilis, Bacteroides thetaiotaomicron, and Clostridium difficile.

**[0024]** Lincomycin derivatives within the scope of this invention include those set forth in Tables I and II as follows:

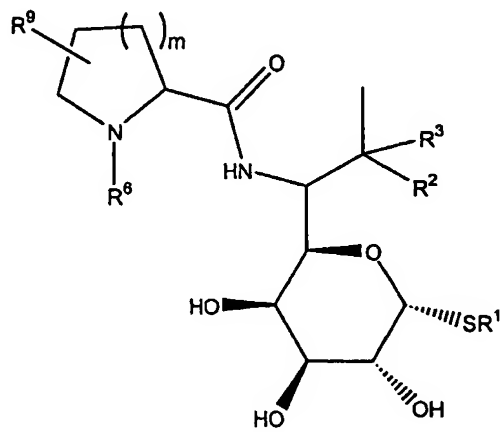


**Table I**

| Ex. # | $R^1$ | $R^2/R^3$ | $R^6$ | $R^{9*}$ | m |
|---|---|---|---|---|---|
| 1 | Methyl | H/methyl | H | ethyl | 2 |
| 2 | Methyl | H/methyl | methyl | propyl | 1 |
| 3 | Methyl | H/cyanomethyl | methyl | propyl | 1 |
| 4 | Methyl | hydroxy/methyl | H | ethyl | 2 |
| 5 | Methyl | hydroxyimino | methyl | propyl | 1 |
| 6 | Methyl | methoxyimino | methyl | propyl | 1 |
| 7 | Methyl | H/methyl | H | butyl | 2 |
| 8 | Methyl | H/methyl | H | pentyl | 1 |
| 9 | Methyl | H/methyl | H | isopentyl | 1 |

* Includes R and/or S isomers as either individual isomers or as a mixture

| Ex. # | $R^1$ | $R^2/R^3$ | $R^6$ | $R^{9*}$ | m |
|---|---|---|---|---|---|
| 10 | Methyl | H/methyl | H | pentyl | 1 |
| 11 | Methyl | fluoro/fluoro | methyl | propyl | 1 |
| 12 | Methyl | fluoro/fluoro | H | pentyl | 1 |
| 13 | Methyl | H/methyl | H | 2-(4-fluorophenyl)ethyl | 1 |
| 14 | Methyl | H/methyl | H | 3,3-difluoropropyl | 1 |
| 15 | Methyl | H/methyl | H | 3-(4-chlorophenyl)propyl | 1 |
| 16 | Methyl | H/methyl | H | 2,2-difluoropentyl | 1 |
| 17 | Methyl | H/methyl | H | propyl | 2 |
| 18 | Methyl | H/methyl | 2-hydroxyethyl | pentyl | 1 |
| 19 | Methyl | H/methyl | 2-methyl-2-hydroxyethyl | pentyl | 1 |
| 20 | Methyl | H/methyl | 2-methyl-2-hydroxyethyl | pentyl | 1 |
| 21 | Methyl | H/methyl | 3-hydroxypropyl | n-pentyl | 1 |
| 22 | Methyl | H/methyl | 2-hydroxyethyl | isopentyl | 1 |
| 23 | Methyl | H/methyl | 2-hydroxyethyl | 3,3-difluoropropyl | 1 |
| 24 | Methyl | fluoro/fluoro | 2-hydroxyethyl | pentyl | 1 |
| 25 | methyl | H/methyl | H | pentyl | 2 |
| 26 | methyl | H/methyl | H | methoxy | 2 |
| 27 | methyl | H/methyl | H | 1-ethylpropyl | 2 |
| 28 | methyl | H/methyl | H | iso-propyl | 2 |
| 29 | methyl | H/methyl | H | butyl | 2 |
| 30 | methyl | H/methyl | H | cyclohexyl | 2 |
| 31 | methyl | H/methyl | 2-hydroxyethyl | ethyl | 2 |
| 32 | methyl | H/methyl | 2-hydroxyethyl | pentyl | 2 |
| 33 | methyl | H/methyl | 2-hydroxyethyl | propyl | 2 |
| 37 | methyl | H/methyl | H | 4,4-difluoropentyl | 1 |
| 38 | methyl | H/methyl | H | 3,3-difluorobutyl | 1 |
| 39 | methyl | H/methyl | H | 3,3-difluoropentyl | 1 |
| 40 | methyl | H/methyl | 2-hydroxyethyl | 3,3-difluoropentyl | 1 |
| 41 | methyl | H/methyl | H | 3,3-difluoropropyl | 2 |
| 42 | methyl | H/methyl | H | 4,4-difluorobutyl | 2 |
| 43 | methyl | H/methyl | H | 5,5-difluoropentyl | 2 |
| 44 | methyl | H/methyl | H | 5-fluoropentyl | 2 |
| 45 | methyl | H/methyl | H | 4-fluorobutyl | 2 |
| 46 | methyl | H/methyl | H | 3-hydroxy-3-ethylpentyl | 2 |
| 47 | methyl | H/methyl | H | butoxy | 2 |

| Ex. # | $R^1$ | $R^2/R^3$ | $R^6$ | $R^{9*}$ | m |
|---|---|---|---|---|---|
| 48 | methyl | H/methyl | H | pentoxy | 2 |
| 49 | methyl | H/methyl | H | 4-fluorobutoxy | 2 |
| 50 | Methyl | R2/R3 = methylene | H | butyl | 1 |
| 51 | methyl | H/methyl | Ethyl | ethyl | 2 |
| 52 | methyl | H/methyl | H | 3-fluoropropoxy | 2 |
| 53 | methyl | H/methyl | H | 3,3,3-trifluoropropoxy | 2 |
| 54 | methyl | H/methyl | H | isobutyl | 2 |
| 55 | methyl | fluoro/fluoro | H | propyl | 2 |
| 56 | methyl | H/methyl | H | fluoro/propyl | 1 |
| 57 | methyl | H/methyl | H | fluoro/butyl | 1 |
| 59 | methyl | H/methyl | H | 2-methoxyethoxy | 2 |
| 60 | methyl | H/methyl | H | butyl | 1 |
| 61 | methyl | H/methyl | H | 4,4-difluoropentyl | 2 |
| 62 | methyl | H/methyl | H | 3-fluoropropyl | 2 |
| 63 | methyl | H/methyl | H | fluoro/propyl | 2 |
| 64 | methyl | H/methyl | H | 2-fluoroethoxy | 2 |
| 66 | Methyl | H/methyl | H | 2-cyclopropyl-ethyl | 2 |
| 67 | Methyl | H/methyl | H | Cyclopropyl-methyl | 2 |
| 68 | Methyl | H/methyl | H | 2-cyclobutyl-ethyl | 2 |
| 69 | Methyl | H/methyl | H | Cyclobutyl-methyl | 2 |
| 70 | Methyl | H/methyl | H | n-butyl | 0 |
| 71 | Methyl | H/methyl | H | Cyclopropyl-methyl | 0 |
| 72 | Methyl | H/methyl | H | Propyl | 0 |
| 73 | Methyl | H/methyl | 2-hydroxy-ethyl | n-butyl | 0 |
| 74 | Methyl | H/methyl | H | n-pentyl | 0 |
| 75 | Methyl | H/methyl | H | Isopentyl | 0 |
| 76 | Methyl | H/methyl | H | 3-cyclobutyl-propyl | 0 |
| 77 | Methyl | H/methyl | H | 2-cyclobutyl-ethyl | 0 |
| 78 | Methyl | H/methyl | H | 2-cyclopropyl-ethyl | 0 |
| 79 | Methyl | H/methyl | H | 3-cyclopropyl-propyl | 0 |
| 80 | Methyl | H/methyl | Methyl | N-butyl | 0 |

| Ex. # | $R^1$ | $R^2/R^3$ | $R^6$ | $R^{9*}$ | m |
|---|---|---|---|---|---|
| 85 | Methyl | H/methyl | H | Cyclopropyl-methyl | 1 |
| 86 | Methyl | H/methyl | H | 2-cyclobutyl-ethyl | 1 |
| 87 | Methyl | H/methyl | H | 2-cyclopropyl-ethyl | 1 |
| 88 | Methyl | H/methyl | H | Propyl | 3 |
| 89 | Methyl | H/methyl | H | *n*-butyl | 2 |
| 90 | Methyl | H/methyl | H | 3-cyclopentyl-propyl | 2 |
| 91 | Methyl | H/methyl | H | 3-methoxy-propyl | 2 |
| 92 | Methyl | H/methyl | H | 3-ethoxy-propyl | 2 |
| 93 | Methyl | H/methyl | H | 3-propoxy-propyl | 2 |
| 94 | Methyl | H/methyl | H | 3-(cyclopropyl-methoxy)-propyl | 2 |
| 95 | Methyl | H/methyl | H | 3-(2-fluoro-ethoxy)-propyl | 2 |
| 96 | Methyl | H/methyl | H | 3-(3-fluoro-propoxy)-propyl | 2 |
| 97 | Methyl | H/methyl | H | 4-methoxy-butyl | 2 |
| 98 | Methyl | H/methyl | H | Propoxy-methyl | 2 |
| 99 | Methyl | H/methyl | H | 3-fluoro-propoxy-methyl | 2 |
| 115 | Methyl | H/methyl | H | Cyclohexyl-methyl | 2 |
| 116 | Methyl | H/methyl | H | 2-propoxy-ethyl | 2 |
| 117 | Methyl | H/methyl | H | cyclopropyl-methoxy | 2 |
| 118 | Methyl | H/methyl | H | Butyl/fluoro | 2 |
| 119 | Methyl | H/methyl | H | ethyl/fluoro | 2 |
| 120 | Methyl | H/methyl | H | 3-fluoropropyl/fluoro | 2 |
| 121 | Methyl | H/methyl | H | 3,3-difluoropropyl/fluoro | 2 |
| 122 | Methyl | H/methyl | H | 2,2-difluoroethoxy-methyl/fluoro | 2 |

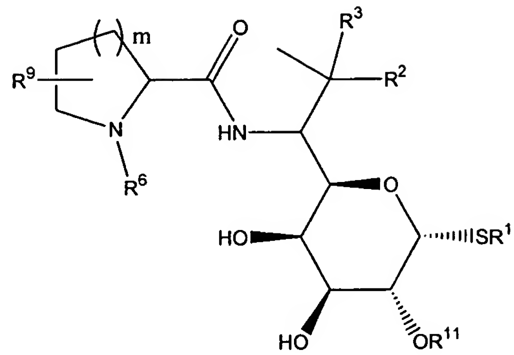


**Table II**

| Ex. # | $R^1$ | $R^2/R^3$ | $R^6$ | $R^{9*}$ | $R^{11}$ | m |
|---|---|---|---|---|---|---|
| 34 | methyl | H/methyl | Fluorenyl-methylene-oxy-carbonyl | Propyl | H | 2 |
| 35 | methyl | H/methyl | Ethoxy-carbonyl | Propyl | H | 2 |
| 36 | methyl | H/methyl | Phenoxy-carbonyl | Propyl | H | 2 |
| 81 | Methyl | H/methyl | H | Propyl | $-PO_3H_2$ | 2 |
| 82 | Methyl | H/methyl | H | Propyl | $-C(O)CH_2CH_2COOH$ | 2 |
| 83 | Methyl | H/methyl | H | Propyl | 2-(*N*-(2-morpholin-4-yl-ethyl)-amino-carbonyl)-ethyl-carbonyl | 2 |
| 84 | Methyl | H/methyl | H | Propyl | *N,N*-dimethyl-amino-methyl-carbonyl | 2 |
| 100 | Methyl | H/methyl | 5-methyl-[1,3]dioxol-2-one-4-yl-methyl | Propyl | H | 2 |
| 101 | Methyl | H/methyl | 5-methyl-[1,3]dioxol-2-one-4-yl-methoxy-carbonyl | Propyl | H | 2 |

* Includes R and/or S isomers as either individual isomers or as a mixture

| | | | | | | |
|---|---|---|---|---|---|---|
| 102 | Methyl | H/methyl | H | Propyl | Pentadecyl-carbonyloxy | 2 |
| 103 | Methyl | H/methyl | 1-methyl-3-oxo-but-1-enyl | Propyl | H | 2 |
| 104 | Methyl | H/methyl | 1-(acetyloxy)-ethyl-oxycarbonyl | Propyl | H | 2 |
| 105 | Methyl | H/methyl | 1-amino-2-methyl-butyl-carbonyl-oxy-methyl-oxycarbonyl | Propyl | H | 2 |
| 106 | Methyl | H/methyl | Piperidin-4-yl-carbonyl-oxy-methyl-oxycarbonyl | Propyl | H | 2 |
| 107 | Methyl | H/methyl | Ethyl-carbonylamino-methyl | Propyl | H | 2 |
| 108 | Methyl | H/methyl | Pyridine-3-yl-carbonylamino-methyl | Propyl | H | 2 |
| 109 | Methyl | H/methyl | 1-amino-ethyl-carbonyl | Propyl | H | 2 |
| 110 | Methyl | H/methyl | 1-amino-2-phenyl-ethyl-carbonyl | Propyl | H | 2 |
| 111 | Methyl | H/methyl | 1-amino-2-methyl-butyl-carbonyl | Propyl | H | 2 |
| 112 | Methyl | H/methyl | 1-amino-2-methyl-propyl-carbonyl | Propyl | H | 2 |
| 113 | Methyl | H/methyl | 1-methyl-1,4 dihydro-pyridin-3-yl- | Propyl | H | 2 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | carbonyl | | | |
| 114 | Methyl | H/methyl | 1-methyl-1,2,3,6 tetrahydro-pyridin-4-yl-oxycarbonyl | Propyl | H | 2 |

**[0025]** As used below, these compounds are named based on acetamide or amide derivatives but, alternatively, these compounds could have been named based on 1-thio-L-threo-β-D-galacto-octopyranoside derivatives. Specific compounds within the scope of this invention include the following compounds:

1-(4-ethylpiperid-6-yl)-*N*-{1- [3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-*n*-propyl-*N*-methylpyrrolidin-2-yl)-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-*n*-propyl-*N*-methylpyrrolidin-2-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methyl-3-cyanoprop-1-yl}acetamide;

1-(4-ethylpiperidyl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-hydroxy-2-methylprop-1-yl}acetamide;

1-(4-*n*-propyl-*N*-methylpyrrolidin-2-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-hydroxyiminoprop-1-yl}acetamide;

1-(4-*n*-propyl-*N*-methylpyrrolidin-2-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methoxyiminoprop-1-yl}acetamide;

1-(3-*n*-butylpiperid-6-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-*n*-pentylpyrrolidin-2-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-[4-(3-methylbut-1-yl)pyrrolidin-2-yl]-*N*-{1- [3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-*n*-propyl-*N*-methylpyrrolidin-2-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2,2-difluoroprop-1-yl}acetamide;

1-(4-*n*-pentylpyrrolidin-2-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2,2-difluoroprop-1-yl}acetamide;

1-(4-(3-*p*-fluorophenyl)prop-1-yl-pyrrolidin-2-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-[4-(3,3-difluoroprop-1-yl)pyrrolidin-2-yl]-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-(3-*p*-chlorophenyl)prop-1-yl-pyrrolidin-2-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-[4-(2,2-difluoropent-1-yl)pyrrolidin-2-yl]-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-*n*-propylpiperid-6-yl)-*N*-{1- [3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide

1-[4-*n*-pentyl-*N*-(2-hydroxyeth-1-yl)pyrrolidin-2-yl]-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-[4-*n*-pentyl-*N*-(2-(*R*)-methyl-2-hydroxyeth-1-yl)pyrrolidin-2-yl]-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-[4-*n*-pentyl-*N*-(2-(*S*)-methyl-2-hydroxyeth-1-yl)pyrrolidin-2-yl]-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-*n*-pentyl-*N*-(3-hydroxyprop-1-yl)pyrrolidin-2-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-[4-(3-methylbut-1-yl)-*N*-(2-hydroxyeth-1-yl)pyrrolidin-2-yl]-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide

1-[4-(3,3-difluoroprop-1-yl)-*N*-(2-hydroxyeth-1-yl)pyrrolidin-2-yl]-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-[4-*n*-pentyl-*N*-(2-hydroxyeth-1-yl)pyrrolidin-2-yl]-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2,2-difluoroprop-1-yl}acetamide;

1-(4-*n*-pentylpiperid-6-yl)-*N*-{[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-methoxypiperid-6-yl)-*N*-{[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-[4-(1-ethylprop-1-yl)piperid-6-yl]-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-*iso*-propylpiperid-6-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-*n*-butylpiperid-6-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-cyclohexylpiperid-6-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-ethyl-*N*-hydroxyethyl-piperid-6-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-*n*-pentyl-*N*-hydroxyethyl-piperid-6-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-*n*-propyl-*N*-hydroxyethyl-piperid-6-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-[4-(4,4-difluoropent-1-yl) pyrrolidin-2-yl]-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-[4-(3,3-difluorobut-1-yl)pyrrolidin-2-yl]-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-[4-(3,3-difluoropent-1-yl)pyrrolidin-2-yl]-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-[4-(3,3-difluoropent-1-yl)-N-(2-hydroxyeth-1-yl)pyrrolidin-2-yl]-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-(3,3-difluoroprop-1-yl)piperid-6-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-(4,4-difluorobut-1-yl)piperid-6-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-(5,5-difluoropent-1-yl)piperid-6-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-(5-fluoropent-1-yl)piperid-6-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-(4-fluorobut-1-yl)piperid-6-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-(3-ethyl-3-hydroxypent-1-yl)piperid-6-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-butoxypiperid-6-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-pentoxypiperid-6-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-(4-fluorobutoxy)piperid-6-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-[4-*n*-butylprop-1-yl)pyrrolidin-2-yl]-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methyl-allyl}acetamide;

1-(4-ethyl-*N*-ethyl-piperid-6-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-(3-fluoropropoxy)piperid-6-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-(3,3,3-trifluoropropoxy)piperid-6-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-*iso*-butylpiperid-6-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-(4-*n*-propylpiperid-6-yl)-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2,2-difluoro-prop-1-yl}acetamide;

1-[4-*n*-propyl-4-fluoro-pyrrolidin-2-yl]-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-[4-*n*-butyl-4-fluoro-pyrrolidin-2-yl]-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

4-(2-methoxyethoxy)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-Butyl-pyrrolidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-(4,4-Difluoro-pentyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-(3-Fluoro-propyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-Fluoro-4-propyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-(2-Fluoroethoxy)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-(2-Cyclopropyl-ethyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-Cyclopropylmethyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-(2-Cyclobutyl-ethyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-Cyclobutylmethyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

3-Butyl-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

3-Cyclopropylmethyl-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

3-Propyl-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

3-Butyl-1-(2-hydroxy-ethyl)-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

3-Pentyl-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

3-(3-Methyl-butyl)-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

3-(3-Cyclobutyl-propyl)-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

3-(2-Cyclobutyl-ethyl)-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

3-(2-Cyclopropyl-ethyl)-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

3-(3-Cyclopropyl-propyl)-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

3-Butyl-1-methyl-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-Cyclopropylmethyl-pyrrolidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-(2-Cyclobutyl-ethyl)-pyrrolidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-(2-Cyclopropyl-ethyl)-pyrrolidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

5-Propyl-azepane-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-butyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-(3-Cyclopentyl-propyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-(3-Methoxy-propyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-(3-Ethoxy-propyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-(3-Propoxy-propyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-(3-Cyclopropylmethoxy-propyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-[3-(2-Fluoro-ethoxy)-propyl]-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-[3-(3-Fluoro-propoxy)-propyl]-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-(4-Methoxy-butyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-Propoxymethyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-(3-Fluoro-propoxymethyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-Cyclohexylmethyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-(2-Propyloxyethyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-Cyclopropylmethoxy-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-Fluoro-4-butyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-Fluoro-4-ethyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-Fluoro-4-(3-fluoropropyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-Fluoro-4-(3,3-difluoropropyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

4-Fluoro-4-(2,2-difluoroethoxymethyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

and prodrugs, tautomers and pharmaceutically acceptable salts thereof.

**[0026]** Specific pro-drug compounds within the scope of this invention include the following compounds:

1-[4-*n*-propyl-*N*-(F-moc)-piperid-6-yl]-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-[4-*n*-propyl-*N*-(carboxylic acid ethyl ester)-piperid-6-yl]-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

1-[4-*n*-propyl-*N*-(carboxylic acid phenyl ester)-piperid-6-yl]-*N*-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide;

Phosphoric acid mono-(4,5-dihydroxy-6-{2-methyl-1-[(4-propyl-piperidine-2-carbonyl)-amino]-propyl}-2-methylsulfanyl-tetrahydro-pyran-3-yl) ester;

Succinic acid mono-(4,5-dihydroxy-6-{2-methyl-1-[(4-propyl-piperidine-2-carbonyl)-amino]-propyl}-2-methylsulfanyl-tetrahydro-pyran-3-yl) ester;

*N*-(2-Morpholin-4-yl-ethyl)-succinamic acid 4,5-dihydroxy-6-{2-methyl-1-[(4-propyl-piperidine-2-carbonyl)-amino]-propyl}-2-methylsulfanyl-tetrahydro-pyran-3-yl ester;

Dimethylamino-acetic acid 4,5-dihydroxy-6-{2-methyl-1-[(4-propyl-piperidine-2-carbonyl)-amino]-propyl}-2-methylsulfanyl-tetrahydro-pyran-3-yl ester;

1-(5-Methyl-2-oxo-[1,3]dioxol-4-ylmethyl)-4-propyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

2-[2-Methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propylcarbamoyl]-4-propyl-piperidine-1-carboxylic acid 5-methyl-2-oxo-[1,3]dioxol-4-ylmethyl ester;

Hexadecanoic acid 4,5-dihydroxy-6-{2-methyl-1-[(4-propyl-piperidine-2-carbonyl)-amino]-propyl}-2-methylsulfanyl-tetrahydro-pyran-3-yl ester;

1-(1-Methyl-3-oxo-but-1-enyl)-4-propyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

2-[2-Methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propylcarbamoyl]-4-propyl-piperidine-1-carboxylic acid 1-acetoxy-ethyl ester;

2-[2-Methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propylcarbamoyl]-4-propyl-piperidine-1-carboxylic acid 2-amino-3-methyl-pentanoyloxymethyl ester;

2-[2-Methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propylcarbamoyl]-4-propyl-piperidine-1-carboxylic acid piperidine-4-carbonyloxymethyl ester;

1-(Propionylamino-methyl)-4-propyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

*N*-{2-[2-Methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propylcarbamoyl]-4-propyl-piperidin-1-ylmethyl}-nicotinamide;

1-(2-Amino-propionyl)-4-propyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

1-(2-Amino-3-phenyl-propionyl)-4-propyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

1-(2-Amino-3-methyl-pentanoyl)-4-propyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

1-(2-Amino-3-methyl-butyryl)-4-propyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

1-(1-Methyl-1,4-dihydro-pyridine-3-carbonyl)-4-propyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide;

2-[2-Methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propylcarbamoyl]-4-propyl-piperidine-1-carboxylic acid 1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl ester;

and tautomers and pharmaceutically acceptable salts thereof.

[0027] The compounds, tautomers, prodrugs and pharmaceutically acceptable salts thereof, as defined herein, may have activity against bacteria, protozoa, fungi, and parasites.

[0028] In another aspect, this invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound defined herein. The pharmaceutical compositions of the present invention may further comprise one or more additional antibacterial agents. One or more of the antibacterial agents may be active against gram negative bacteria. One or more of the antibacterial agents may be active against gram positive bacteria.

[0029] In one of its method aspects, this invention is directed to a method for the treatment of a microbial infection in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of this invention. The compound of this invention may be administered to the mammal orally, parenterally, transdermally, topically, rectally, or intranasally.

[0030] In another of its method aspects, this invention is directed to a method for the treatment of a microbial infection in a mammal comprising administering to the mammal a pharmaceutical composition comprising a therapeutically effective amount of a compound of this invention. The pharmaceutical compositions of the present invention may further comprise one or more additional antibacterial agents, one of which may be active against gram negative bacteria and/or one of which may be active against gram positive bacteria. The pharmaceutical composition may be administered to the mammal orally, parenterally, transdermally, topically, rectally, or intranasally.

[0031] In a preferred embodiment, the microbial infection being treated is a gram positive bacterial infection. In an additional embodiment, the infection may be a gram negative bacterial infection. In a further embodiment, the infection may be a mycobacteria infection, a mycoplasma infection, or a chlamydia infection.

[0032] In yet another aspect, the present invention provides novel intermediates and processes for preparing compounds of formula (I), (II), (III) and (IV).

## DETAILED DESCRIPTION OF THE INVENTION

[0033] As described above, this invention relates to lincomycin derivatives that exhibit antibacterial activity, in particular gram positive antibacterial activity. However, prior to describing this invention in further detail, the following terms will first be defined.

Definitions

[0034] Unless otherwise stated, the following terms used in the specification and claims have the meanings given below.

[0035] "Acyl" means the group -C(O)R' wherein R' is alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl.

[0036] "Acyloxy" means the group –C(O)OR', wherein R' is alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl.

[0037] "Alkenyl" means a linear unsaturated monovalent hydrocarbon radical of two to eight carbon atoms or a branched monovalent hydrocarbon radical of three to eight carbon atoms containing at least one double bond, (-C=C-). Examples of alkenyl groups include, but are not limited to, allyl, vinyl, 2-butenyl, and the like.

[0038] "Alkoxy" refers to the group "alkyl-O-" which includes, by way of example, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, 1,2-dimethylbutoxy, and the like.

[0039] "Alkoxyalkoxy" refers to the group alkyl-O-alkylene-O-, wherein alkyl is as defined herein.

[0040] "Alkyl" means a linear saturated monovalent hydrocarbon radical of one to eight carbon atoms or a branched saturated monovalent hydrocarbon radical of three to eight carbon atoms. Examples of alkyl groups include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, and the like.

[0041] "Alkylene" means a linear divalent hydrocarbon radical of one to eight carbon atoms or a branched divalent hydrocarbon group of three to eight carbon atoms. Examples of alkylene groups include, but are not limited to, methylene, ethylene, 2-methylpropylene, and the like.

[0042] "Alkylthio" refers to the group "alkyl-S-" which includes, by way of example, methylthio, butylthio, and the like.

[0043] "Alkynyl" means a linear monovalent hydrocarbon radical of two to eight carbon atoms or a branched monovalent hydrocarbon radical of three to eight carbon atoms containing at least one triple bond, (-C≡C-). Examples of alkynyl groups include, but are not limited to, ethynyl, propynyl, 2-butynyl, and the like.

[0044] "Amino" or "substituted nitrogen" refers to the group "$-NR_aR_b$" wherein $R_a$ and $R_b$ are independently H, alkyl, haloalkyl, alkenyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl.

[0045] "Aminocarboxyalkyl" means a group "$-R_cC(O)NR_aR_b$" where $R_c$ is an alkylene, as defined above, and $R_a$ and $R_b$ are as defined above.

[0046] "Aryl" means a monovalent monocyclic or bicyclic aromatic carbocyclic group of six to fourteen ring atoms. Examples include, but are not limited to, phenyl, naphthyl, and anthryl. The aryl ring may be optionally fused to a 5-, 6-, or 7-membered monocyclic non-aromatic ring optionally containing 1 or 2 heteroatoms independently selected from oxygen, nitrogen, or sulfur, the remaining ring atoms being C where one or two C atoms are optionally replaced by a carbonyl. Representative aryl groups with fused rings include, but are not limited to, 2,5-dihydro-benzo[b]oxepinyl, 2,3-dihydrobenzo[1,4]dioxanyl, chromanyl, isochromanyl, 2,3-dihydrobenzofuranyl, 1,3-dihydroisobenzofuranyl, benzo[1,3]dioxolyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1H-indolyl, 2,3dihydro-1H-isoindolyl, benzimidazole-2-onyl, 2-H-benzoxazol-2-onyl, and the like.

[0047] "Carbonyl" means the group "C(O)."

[0048] "Carboxy" means the group "C(O)O."

[0049] "Cyanoalkyl" refers to an alkyl, wherein alkyl is as defined above, substituted with one or more cyano (-CN) groups provided that if two cyano groups are present they are not both on the same carbon atom. Examples of cyanoalkyl groups include, for example, cyanomethyl, 2-cyanoethyl, 2-cyanopropyl, and the like.

[0050] "Cycloalkyl" refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single or multiple cyclic rings including, by way of example, cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, adamantanyl, and the like. Cycloalkyl groups of the present invention also include fused multicyclic rings wherein one or more of the rings within the multicyclic ring system are aromatic, as long as the point of attachment to the core or backbone of the structure is on the non-aromatic ring, e.g., fluorenyl.

[0051] "Cycloalkylalkyl" means a group $-R_cR_d$ where $R_c$, is an alkylene group and $R_d$ is a cycloalkyl group, as defined above. Examples include, but are not limited to, cyclopropylmethylene, cyclohexylethylene, and the like.

[0052] "Halo" or "Halogen" means fluoro, chloro, bromo, or iodo.

[0053] "Haloalkyl" means an alkyl, wherein alkyl is as defined above, substituted with one or more, preferably one to 6, of the same or different halo atoms. Examples of haloalkyl groups include, for example, trifluoromethyl, 3-fluoropropyl, 2,2-dichloroethyl, and the like.

[0054] "Heteroaryl" means a monovalent monocyclic or bicyclic aromatic radical of 5 to 10 ring atoms containing one, two, or three ring heteroatoms selected from N, O, or S, the

remaining ring atoms being C. Representative examples include, but are not limited to, thienyl, benzothienyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinolinyl, quinoxalinyl, imidazolyl, furanyl, benzofuranyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, 2-pyridonyl, 4-pyridonyl, N-alkyl-2-pyridonyl, pyrazinonyl, pyridazinonyl, pyrimidinonyl, oxazolonyl, and the like.

**[0055]** "Heterocycle" or "heterocyclic" refers to a saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 10 carbon atoms and from 1 to 4 heteroatoms selected from the group consisting of nitrogen, sulfur, or oxygen within the ring, wherein, in fused ring systems one or more of the rings can be aryl or heteroaryl as defined herein. Examples of heterocycles and heteroaryls include, but are not limited to, azetidine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, dihydroindole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydro-isoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazole, thiazolidine, thiophene, benzo[b]thiophene, morpholinyl, thiomorpholinyl (also referred to as thiamorpholinyl), piperidinyl, pyrrolidine, tetrahydrofuranyl, and the like.

**[0056]** Heterocycles may be optionally substituted with from one to three substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, alkoxy, acyloxy, amino, hydroxyl, carboxy, cyano, oxo, nitro, and alkylthio as these terms are defined herein.

**[0057]** "Hydroxy" or "hydroxyl" means the group -OH.

**[0058]** "Hydroxyalkyl" refers to an alkyl, wherein alkyl is as defined above substituted with one or more -OH groups provided that if two hydroxy groups are present they are not both on the same carbon atom. Examples of hydroxyalkyl groups include, for example, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, and the like.

**[0059]** "Mammal" refers to all mammals including humans, livestock, and companion animals.

**[0060]** "Optional" or "optionally" means that the subsequently described event or circumstance may, but need not, occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "aryl group optionally mono- or di- substituted with an alkyl group" means that the alkyl may but need not

be present, and the description includes situations where the aryl group is mono- or disubstituted with an alkyl group and situations where the aryl group is not substituted with the alkyl group.

[0061] "Pharmaceutically acceptable carrier" means a carrier that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable carrier" as used in the specification and claims includes both one and more than one such carrier.

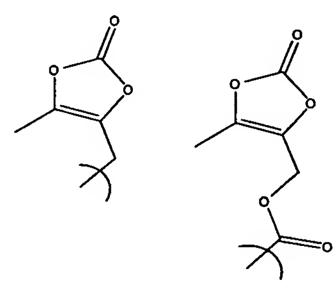
[0062] "Pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include, but are not limited to,

(1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-l-carboxylic acid, glucoheptonic acid, 4,4'methylenebis-(3-hydroxy-2-ene-l-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or

(2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth metal ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

[0063] "Prodrugs" mean any compound which releases an active parent drug according to a compound of the subject invention in vivo when such prodrug is administered to a mammalian subject. Prodrugs of a compound of the subject invention are prepared by modifying functional groups present in a compound of the subject invention in such a way that the modifications may be cleaved in vivo to release the parent compound. Prodrugs include compounds of the subject

invention wherein a hydroxy, sulfhydryl or amino group in the compound is bonded to any group that may be cleaved in vivo to regenerate the free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate, and benzoate derivatives), carbamates (e.g., N,N-dimethylaminocarbonyl) of hydroxy functional groups in compounds of the subject invention, and the like. Specific examples include -C(O)O-alkylene-cycloalkyl, -C(O)O-alkylene-substituted cycloalkyl, -C(O)O-alkyl, -C(O)O-substituted alkyl, -C(O)O-aryl, -C(O)O-substituted aryl, -C(O)O-heteroaryl, -C(O)O-substituted heteroaryl, -$[C(O)O]_p$-alkylene-heterocycle, -$[C(O)O]_p$-alkylene-substituted heterocycle, wherein p is 0 or 1. In one embodiment, the -C(O)O-substituted alkyl does not include the following:



[0064] "Substituted alkyl" means an alkyl group, as defined above, in which one or more of the hydrogen atoms has been replaced by a halogen (i.e., Cl, Br, F, or I), oxygen, hydroxy, amine (primary), amine (secondary-amine substituted by alkyl above), amine (tertiary-amine substituted by alkyl as above), sulfur, -SH, phenyl, substituted phenyl, cycloalkyl, alkoxy, substituted alkoxy. Examples of substituted alkyl groups include, but are not limited to, 1-fluoroethyl, 1-chloroethyl, 2-fluoroethyl, 2-chloroethyl, 1-bromopropyl, 2-iodopropyl, 1-chlorobutyl, 4-flurobutyl, 4-chlorobutyl, 2-cyclopropyl-ethyl, 3-cyclobutyl-propyl, 4-cyclopentyl-butyl, and 4-cyclohexyl-butyl.

[0065] "Substituted alkoxy" means substituted alkyl-O-, wherein substituted alkyl is as defined herein.

[0066] "Substituted aryl" means an aryl ring substituted with one or more substituents, preferably one to three substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, alkoxy, acyloxy, amino, hydroxy, carboxy, cyano, nitro, alkylthio, and thioalkyl. The aryl ring may be optionally fused to a 5-, 6-, or 7-membered monocyclic non-aromatic ring optionally containing 1 or 2 heteroatoms independently selected from oxygen, nitrogen, or

sulfur, the remaining ring atoms being carbon where one or two carbon atoms are optionally replaced by a carbonyl.

[0067] "Substituted cycloalkyl" means a cycloalkyl substituted with an alkyl group, wherein alkyl is as defined above or a group as defined above for substituted alkyl.

[0068] "Substituted heteroaryl" means a heteroaryl ring, wherein heteroaryl is as defined above, substituted with one or more substituents, preferably one to three substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, alkoxy, acyloxy, amino, hydroxy, carboxy, cyano, nitro, alkylthio, and thioalkyl, wherein said substituents are as defined herein.

[0069] "Substituted oxygen" refers to the group "-O-$R^d$" wherein $R^d$ is alkyl, haloalkyl, alkenyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl, wherein said substituents are as defined herein.

[0070] "Substituted phenyl" means a phenyl ring wherein one or more of the hydrogen atoms has been replaced by a halogen, hydroxy, alkyl, amine (primary, secondary, and tertiary with the latter two alkyl substituted), -SH, and phenyl. Representative examples include, but are not limited to, p-bromophenyl, m-iodophenyl, o-chlorophenyl, p-ethylphenyl, m-propylphenyl, o-methylphenyl, and p-octylphenyl.

[0071] "Thioalkyl" refers to an alkyl, wherein alkyl is as defined above, substituted with one or more -SH groups provided that if two hydroxy groups are present they are not both on the same carbon atom. Examples of thioalkyl groups include, for example, thiomethyl, 2-thioethyl, 2-thiopropyl, and the like.

[0072] "Therapeutically effective amount" means the amount of a compound or composition that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound or composition, the disease and its severity and the age, weight, etc., of the mammal to be treated.

[0073] "Treating" or "treatment" of a disease includes:

(1) preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease,

(2) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms, or

(3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

"Tautomer" refers to an isomer in which migration of a hydrogen atom results in two or more structures.

[0074] The compounds of the present invention are generally named according to the IUPAC or CAS nomenclature system. Abbreviations that are well known to one of ordinary skill in the art may be used (e.g. "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "Bn" for benzyl, "h" for hour and "rt" for room temperature).

General Synthetic Schemes

[0075] Compounds of this invention can be made by the methods depicted in the reaction schemes shown below.

[0076] The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Toronto Research Chemicals (North York, ON Canada), Aldrich Chemical Co. (Milwaukee, Wisconsin, USA), Bachem (Torrance, California, USA), Emka-Chemie, or Sigma (St. Louis, Missouri, USA) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

[0077] As it will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups, as well as suitable conditions for protecting and deprotecting particular function groups are well known in the art. For example, numerous protecting groups are described in T.W. Greene and G.M. Wuts, Protecting Groups in Organic Synthesis, Second Edition, Wiley, New York, 1991, and references cited therein.

[0078] The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography, and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

[0079] The compounds of this invention will typically contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers. All such stereoisomers (and enriched mixtures) are included within the scope of this invention, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents, and the like.

Preparation of Compounds of formula (I)

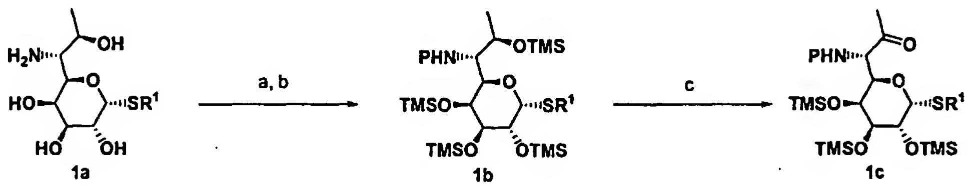
[0080] In general, to prepare the compounds of formula (I) of the present invention, an appropriately 7-substitituted lincosamine intermediate and an appropriately substituted pyrrolidinyl or piperidyl carboxylic acid are condensed under reactive conditions, preferably in an inert organic solvent, in the presence of a coupling reagent and an organic base. This reaction can be performed with any number of known coupling reagents, such as O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), 1-hydroxybenzotriazole hydrate (HOBT) with carbodiimides, isobutyl chloroformate, diphenylphosphoryl azide (DPPA), and the like. Suitable organic bases include diisopropylethylamine (DIEA), triethylamine (TEA), pyridine, N-methyl morpholine, and the like. Suitable inert organic solvents which can be used include, for example, N,N-dimethylformamide, acetonitrile, dichloromethane, and the like. This reaction is typically conducted using an excess of carboxylic acid to lincosamine at temperatures in the range of about 0°C to about 50°C. The reaction is continued until completion, which typically occurs in from about 2 to 12 h.

[0081] Appropriately 7-substitituted lincosamine intermediates, as defined in the present invention (i.e., $R^2/R^3$), are synthesized by methods well known to those of skill in the art from methyl 6-amino-6,8-dideoxy-1-thio-erythro-β-D-galacto-octopyranoside, which can be prepared as described by Hoeksema, et al., Journal of the American Chemical Society, **1967**, 89 2448-2452. Illustrative syntheses for 7-substituted lincosamine intermediates are shown below in Schemes 1-5.

[0082] Appropriately substituted pyrrolidinyl or piperidyl carboxylic acid intermediates, as defined in the present invention (i.e., $R^9$), are also synthesized by methods well known to those of skill in the art from prolines and pyridines. The prolines and pyridines that can be used in the synthesis of the carboxylic acid intermediates of the present invention include, for example, 4-oxoproline and 4-substituted pyridines. The prolines and pyridines used in the synthesis are

commercially available from vendors such as Aldrich and Sigma. Alternatively, these prolines and pyridines can be prepared by methods well known in the art. Illustrative syntheses for appropriately substituted pyrrolidinyl or piperidyl carboxylic acid intermediates are shown below in Schemes 6-10.

[0083] Scheme 1 below illustrates a general synthesis of a lincosamine intermediate **1c** wherein P is an N-protecting group, preferably either Cbz or Boc, and $R^1$ is as defined for formula (I).



**Scheme 1.** General synthesis of lincosamine intermediate **1c.**

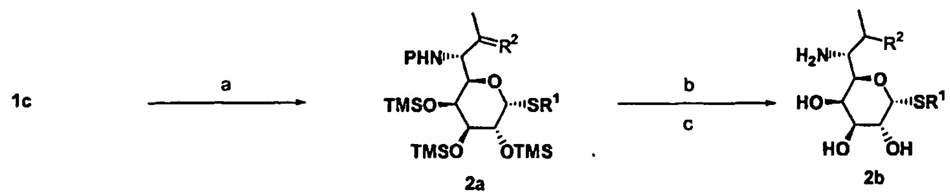
(a) N-Protection (Boc, Cbz); (b) O-silyl protection (TMS); (c) Swern oxidation.

[0084] As shown in Scheme 1, methyl 6-amino-6,8-dideoxy-1-thio-erythro-β-D-galacto-octopyranoside, **1a,** is prepared as described by Hoeksema, et al., Journal of the American Chemical Society, **1967**, 89 2448-2452. The amino functional group and the hydroxy functional groups of the product **1a** are then protected with suitable protecting groups. Suitable N-protecting groups can be formed by the addition of di-t-butyldicarbonate, N-(benzyloxycarbonyloxy) succinimide, and the like. The hydroxy groups can be protected as silyl ethers. The hydroxyl group can be converted to trimethylsilyl (TMS) ethers by reaction with N, O-bis-(trimethylsilyl)trifluoroacetamide in the presence of an appropriate organic base such as triethylamine (TEA) or trimethylsilyl chloride in the presence of an organic base such as triethylamine. The N-protection is typically accomplished before the O-protection. Chromatography of the crude product on silica after evaporation of the solvent provides the protected product **1b**.

[0085] The 7-O-trimethylsilyl group of **1b** is chemoselectively deprotected and oxidized to provide the 7-keto-lincosamine derivative **1c**. This selective transformation is performed by addition of the protected product **1b** to dimethylsulfoxide and oxalyl chloride in an inert organic solvent such as dichloromethane followed by an appropriate organic base such as triethylamine. Alternatively, the transformation may be performed by addition of **1b** to dimethyl sulfoxide and an appropriate activating agent such as trifluoroacetic anhydride in an inert organic solvent. The reaction is typically conducted at temperatures in the range of approximately -70°C to 80°C.

The resulting reaction mixture is stirred at the low temperature and is then allowed to warm to approximately -50°C. The reaction is maintained at this second temperature for approximately 1 h to 3 h. To the reaction mixture is added a suitable organic base, such as TEA, pyridine, and the like. The reaction mixture is appropriately worked up to provide the product **1c**. The general class of conditions used in the transformation of **1b** to **1c** is known in the art as Swern oxidation conditions.

[0086] Scheme 2 below illustrates a general synthesis of a lincosamine intermediate **2b** wherein P is an N-protecting group, preferably either Cbz or Boc, $R^1$ is as defined for formula (I), and one of $R^2$ and $R^3$ is hydrogen and the other is as defined for formula (I).




**Scheme 2.** General synthesis of lincosamine intermediate **2b**.

(a) Wittig olefination ($R^2PPh_3^+X^-$, $R^2PO(OEt)_2$, base, solvent); (b) and (c) $H_2/Pd$, Global de-protection

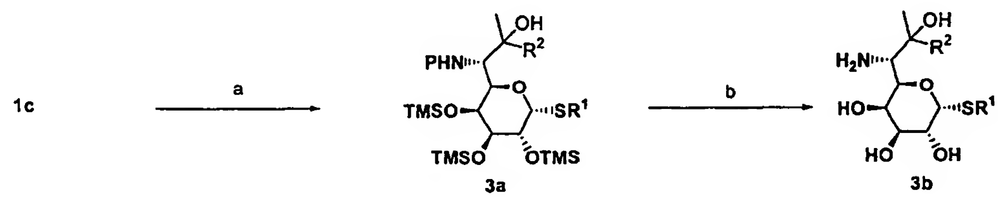
[0087] As shown in Scheme 2, a keto-lincosamine intermediate **1c** is reacted to form an alkene using the Wittig or Homer-Wadsworth-Emmons reaction. In this reaction, a suitable phosphonium salt or phosphonate is deprotonated using a strong base to form a phosphorus ylide. Suitable phosphonium salts which can be used are alkyltriphenylphosphonium halides, which can be prepared by the reaction of triphenylphosphine and an alkyl halide. Suitable phosphorous compounds include, for example, methyltriphenylphosphonium bromide, diethyl(cyanomethyl)phosphonate and the like. Suitable strong bases which can be used to form the ylide include organolithium reagents, potassium tert-butoxide, and the like. The formation of the phosphorus ylide is typically conducted under an inert atmosphere, such as $N_2$, in an inert organic solvent such as toluene, THF, and the like, at low temperatures.

[0088] After formation of the phosphorus ylide, the product **1c** is added to the reaction. The reaction conveniently can be performed at temperatures between -40°C and room temperature and is stirred until completion, typically 1 to 4 h. The resulting organic solution is worked-up and chromatography of the crude product on silica provides the alkene product **2a**.

[0089] Optionally, the product of **2a** may be purified using conventional techniques, such as chromatography and said purified product may be used in the subsequent coupling reaction to yield vinyl lincosamine derivatives of the present invention.

[0090] The product **2a** is then hydrogenated to provide the saturated product **2b**. The hydrogenation is typically performed in a polar organic solvent such as methanol, ethanol, and the like, using 10% palladium on carbon in a Parr bottle. The bottle is purged, and charged with $H_2$ to approximately 50 to 70 psi and shaken until completion, typically approximately 12 to 24 h. The resulting reaction mixture is filtered, e.g., through celite, and rinsed with a polar organic solvent such as methanol. The organic solution is worked up by transferring to a resin funnel containing dry, washed Dowex 50w-400x $H^+$ form and shaken. After washing the resin with methanol and water, the product **2b** is eluted from the resin by washing with 5% TEA in MeOH. The product can also be purified by silica gel column chromatography.

[0091] Scheme 3 illustrates a general synthesis of a lincosamine intermediate **3b** wherein P is an N-protecting group, preferably either Cbz or Boc, $R^1$ is as defined for formula (I), and one of $R^2$ or $R^3$ is alkyl and the other is -OH.

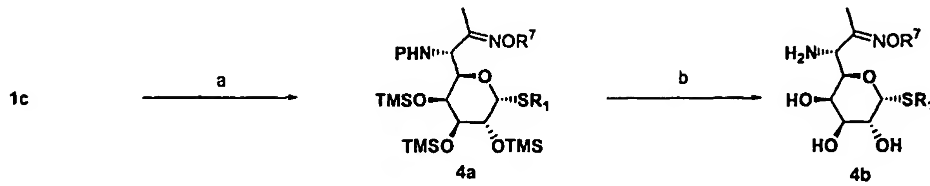



**Scheme 3.** General synthesis of lincosamine intermediate **3b**.

(a) $R^2M$ (carbon nucleophile); (b) (i) TMS de-protection ($H^+$ or F-) and (ii) N-deprotection

[0092] As shown in Scheme 3, suitable carbon nucleophiles add to 7-ketolincosamine intermediate **1c** in suitable inert organic solvents to provide a 7-hydroxy lincosamine intermediate **3b**. Suitable carbon nucleophiles include methylmagnesium chloride, diethyl zinc, sodium acetylide and the like and suitable inert organic solvents which can be used include THF, diethyl ether, toluene, and the like. The reaction is typically conducted at reduced temperatures, approximately at 0°C, for about 3 to 5 h. The reaction is then quenched with a saturated aqueous acidic solution, such as saturated aqueous $NH_4Cl/H_2O$. The quenched mixture is then worked up and can be purified by chromatography to provide the product **3b**.

[0093] Scheme 4 below illustrates a general synthesis of a lincosamine intermediate **4b** wherein P is a N-protecting group, preferably Boc, $R^1$ is as defined for formula (I), and $R^2/R^3$ is an oxime ($=NOR^7$), wherein $R^7$ is as defined for formula (I).

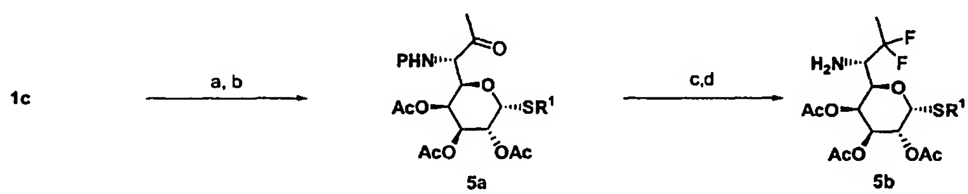


**Scheme 4.** General synthesis of 7-oxime-lincosamines **4b**.

**[0094]** As shown in Scheme 4, the lincosamine intermediate **1c** is converted to the oxime by stirring in the presence of a suitable reagent such as O-trimethylsilylhydroxylamine, O-alkylhydroxylamine hydrochloride (for example, O-methylhydroxylamine hydrochloride), and the like. The reaction is typically conducted in a polar organic solvent such as methanol. The reaction conveniently can be conducted at rt in approximately 8 to 24 h. The solvent is removed to provide the N-protected product **4a**.

**[0095]** Removal of the protecting group can be carried out with acids, such as trifluoroacetic acid (TFA), hydrochloric acid, p-toluenesulfonic acid, and the like, in an inert organic solvent such as dichloromethane, dichloroethane, dioxane, THF, and the like. The removal is typically conducted at low temperatures, e.g., 0°C, and then gradually allowed to warm to room temperature to provide the product **4b**.

**[0096]** Scheme 5 below illustrates a general synthesis of a lincosamine intermediate **5b** wherein $R^2$ and $R^3$ are both fluorine, P is an N-protecting group, preferably Cbz or Boc, and $R^1$ is as defined for formula (I).



**Scheme 5.** General synthesis of 7-deoxy-7,7-difluorolincosamines **5b**.

(a) $F^-$; (b) $Ac_2O$, pyridine, DMAP; (c) DAST; (d) TFA

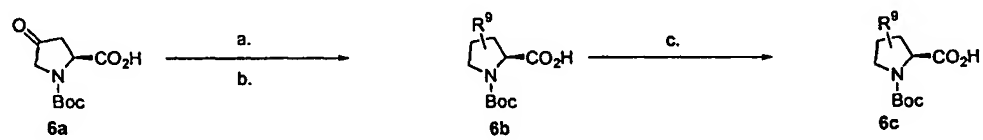
**[0097]** As shown in Scheme 5, the lincosamine intermediate **1c** is contacted with a suitable fluoride in an inert organic solvent. Suitable fluorides which can be used include tetrabutylammonium fluoride, Amberlite resin A-26 F form, HF•pyridine and the like. Suitable inert organic solvents include THF, acetonitrile, dichloromethane, dioxane, and the like. The reaction conveniently can be conducted at rt in about 1 to 2 h. The product (not shown) can be purified on a silica gel column.

[0098] The O-protecting groups on the product obtained from the column are converted by contact with acetic anhydride and dimethylaminopyridine (DMAP) in a suitable mixture of an inert organic solvent and an organic base, such as, for example, dichloromethane and pyridine. The reaction conveniently can be conducted at rt in approximately 6 to 12 h. The product can be purified on silica gel column to provide product **5a**.

[0099] The product **5a** is contacted with a suitable fluorinating reagent and then the N-protecting group is removed to provide the product **5b**. Suitable fluorinating reagents which can be used include, for example, dimethylaminosulfurtrifluoride, [bis(2-methoxyethyl)amino]sulfurtrifluoride, and the like. The reaction is typically conducted in an inert organic solvent such as dichloromethane, ethylacetate, THF, and the like at room temperature in approximately 6 to 12 h.

[0100] Removal of the protecting group can be carried out with acids, such as trifluoroacetic acid (TFA), hydrochloric acid, p-toluenesulfonic acid, and the like, in an inert organic solvent such as dichloromethane, dichloroethane, dioxane, THF, and the like. The removal is typically conducted at low temperatures, e.g., 0°C, and then gradually allowed to warm to room temperature to provide the product **5b**.

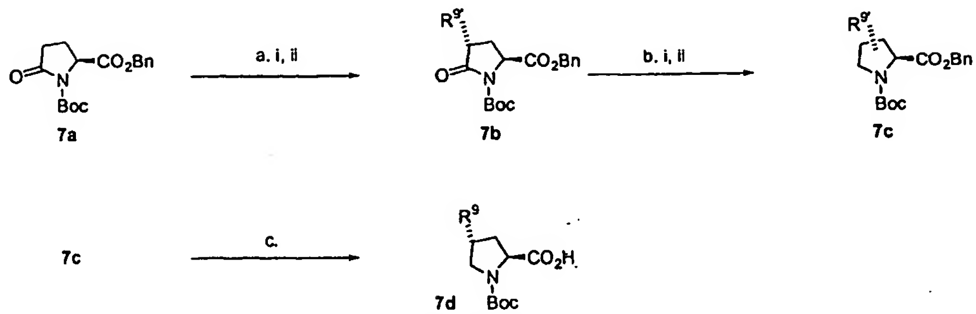
[0101] Scheme 6 below illustrates a general synthesis of a proline intermediate **6c** wherein $R^9$ is as defined for formula (I).




**Scheme 6.** General synthesis of cis/trans $R^9$-proline intermediate mixtures **6c**.
(a) $R^9CH_2Br+Ph_3P$ , NaH, DMSO; (b) $H_2/Pt$

[0102] As shown in Scheme 6, the product **6c** is prepared as described in Birkenmeyer, et al., Journal of Medicinal Chemistry **1972**, 15, 1255-1259. Compound **6a** is commercially available from vendors such as RSP (Scientific Research Consortium, Inc.). Alternatively, **6a** can be prepared from commercially available protected hydroxy prolines by methods well known in the art. See, e.g., Demange, et al., Tetrahedron Letters **1998**, 39,1169-1172.

[0103] Scheme 7 below illustrates a general synthesis of trans-$R^9$-proline intermediates **7d**, wherein $R^9$ is alkyl or substituted alkyl.



**Scheme 7.** General synthesis of trans-alkylprolines **7d**.

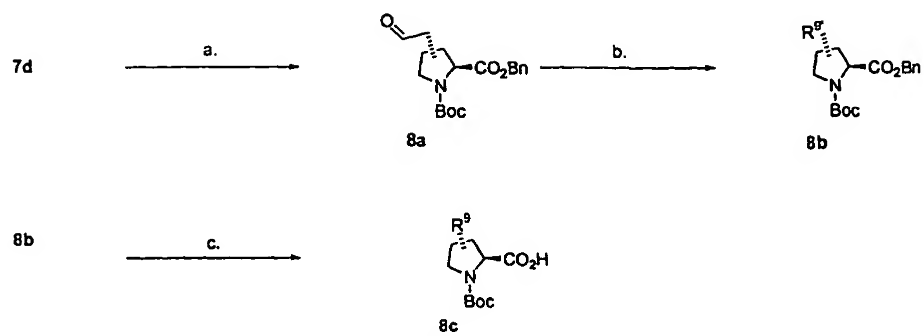
(a) (i) LiHMDS, THF -78°C, (ii) bromoalkene; (b) (i) $LiBHEt_3$, THF -78°C, (ii) $BF_3OEt_2$, $Et_3SiH$; (c) H2 Pd/C.

**[0104]** As shown in Scheme 7, a protected 4-oxoproline, **7a,** is enolated with a suitable enolation agent and then alkylated with a suitable alkylating agent in an inert organic solvent to provide a lactam **7b** (wherein $R^{9'}$ is alkenyl), as described in the literature procedure by Zhang, et al., J.A.C.S. **1998**, 120 3894-3902. Compound **7a** is commercially available from vendors such as Bachem. Alternatively, **7a** can be prepared by methods well known in the art. Suitable enolating agents include LiHMDS, $LiN(iPr)_2$, and the like, and suitable alkylating agents include allylic and benzylic bromides, for example, 4-bromo-2-methyl-2-butene and cis-1-bromo-2-pentene, allylbromide, and the like.

**[0105]** The lactam **7b** is reduced using a suitable reducing agent to provide a pyrrolidine **7c**, wherein $R^{9'}$ is alkenyl. The reduction is preformed by a two-step sequence involving superhydride reduction of the lactam to the hemiaminal and the subsequent reduction of the hemiaminal. Suitable reducing agents which can be used include $Et_3SiH/BF_3{\cdot}OEt_2$, $Et_3SiH/TiCl_4$, and the like.

**[0106]** The pyrrolidine **7c** is then hydrogenated to simultaneously remove the unsaturation in the $R^{9'}$ substituent and remove the benzyl protecting group from the carboxylic acid to provide the product **7d**. The hydrogenation is typically performed in a polar organic solvent such as methanol, ethanol, and the like, using 10% palladium on carbon in a Parr bottle. The bottle is purged, and charged with $H_2$ to approximately 50 to 70 psi and shaken until completion, typically approximately 5 to 24 h. The reaction mixture is filtered, e.g., through a celite pad, and washed with a polar organic solvent, such as methanol. Evaporation of the combined washings and filtrate affords the product **7d**, wherein $R^9$ is an alkyl or substituted alkyl.

**[0107]** Scheme 8 below illustrates a general synthesis of trans-$R^9$-proline intermediates **8c**, wherein $R^9$ is alkyl or substituted alkyl.



Scheme 8. General synthesis of trans-$R^9$-substituted prolines **8c**, wherein $R^9$ is alkyl or substituted alkyl.

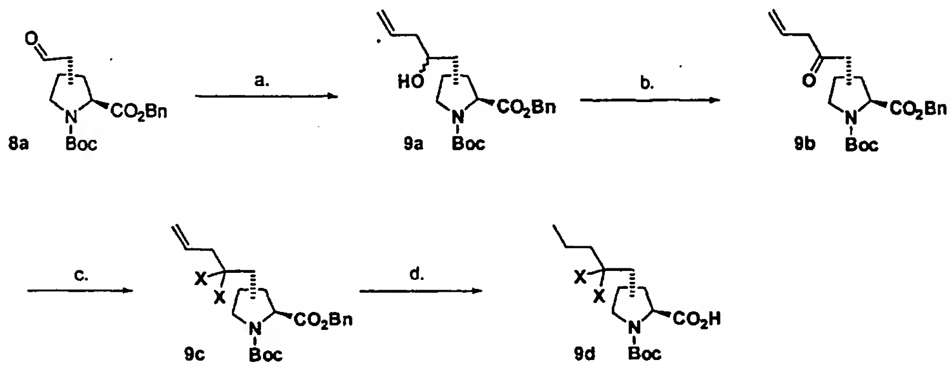
(a) $O_3$, DCM, -78°C, DMS; (b) $P^+Ph_3$ salt, Base; (c) $H_2$, Pd/C.

**[0108]** As shown in Scheme 8, the product **7d** is ozonolized to provide the aldehyde **8a**. The ozonolysis reaction is typically conducted in an anhydrous inert organic solvent, such as dichloromethane, dioxane, THF, and the like, at low temperatures, e.g., -78°C followed by quenching of the reaction with a reducing agent such as DMS, $Ph_3P$.

**[0109]** The aldehyde, **8a**, is reacted with a suitable phosphonium salt in the presence of a strong base in an inert organic solvent. Suitable phosphonium salts which can be used include, for example, fluorobenzyl phosphonium chloride, 4-chlorobenzyl phosphonium chloride, dibromofluoromethane and triphenylphosphine, and the like. Suitable bases which can be used include potassium t-butoxide, organolithium reagents, and activated zinc. Suitable organic solvents which can be used include toluene, THF, dimethylacetamide, and the like. The reaction is typically conducted in an inert atmosphere, such as under nitrogen, with vigorous stirring. The reaction is typically conducted at rt to approximately 110°C for 1 to 2 h. The resulting reaction mixture is appropriately worked-up and can be purified by chromatography to provide **8b** (wherein $R^{9'}$ is alkenyl).

**[0110]** The product **8b** is then hydrogenated to provide the product **8c**. The hydrogenation is typically performed in a polar organic solvent such as methanol, ethanol, and the like, using 10% Palladium on carbon in a Parr bottle. The bottle is purged, and charged with $H_2$ to approximately 40 to 70 psi and shaken until completion, typically approximately 4 to 24 h. The reaction mixture is filtered, e.g., through a celite pad and washed several times with a polar organic solvent, such as methanol. Evaporation of the combined washings and filtrate affords the product **8c**, wherein $R^9$ is an alkyl or substituted alkyl.

[0111] Scheme 9 below illustrates a general synthesis of trans-$R^9$-proline intermediates **9d**, wherein $R^9$ is substituted alkyl wherein X is halo.




**Scheme 9.** Example synthesis of trans-halosubstituted alkyl prolines **9d**.

(a) Tetraallyltin, $BF_3$•$Et_2O$; (b) DMSO, $(COCl)_2$, TEA; (c) DAST (d)10% Pd/C, $H_2$

[0112] As shown in Scheme 9, aldehyde, **8a**, is reduced and alkylated using a suitable reagent in an inert organic solvent to provide a hydroxyalkenyl substituted proline, **9a**. Suitable reagents to reduce and alkylate the aldehyde include tetraallyltin/boron trifluoride etherate, allylTMS/boron trifluoride etherate and suitable inert organic solvents which can be used include THF, dichloromethane, and the like. The reaction is typically conducted at low temperatures, e.g., 0°C, for approximately 1 to 2 h. To the reaction mixture is added a solution of a suitable fluoride salt in water, for example potassium fluoride in water, followed by the addition of methanol. The reaction mixture is filtered, for example, over celite. The product can be purified by chromatography to provide **9a**.

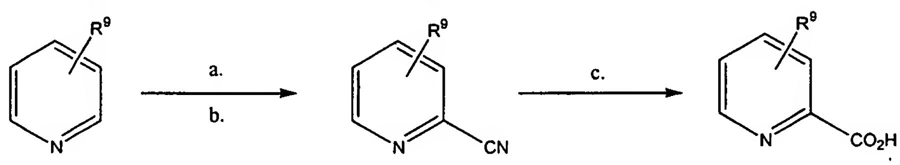
[0113] The hydroxyalkenyl substituted proline, **9a**, is oxidized to the ketone by contact with a suitable oxidizing agent in an inert organic solvent. Suitable oxidizing agents include oxalyl chloride/DMSO, Dess Martin periodinane, and the like. Suitable inert organic solvents include dichloromethane, and the like. The reaction is typically conducted at reduced temperatures, e.g., -72°C to -50°C, for approximately 30 min to 2 h. To the reaction mixture is added a suitable organic base, such as triethylamine. The reaction mixture is worked up to provide product **9b**.

[0114] The keto-substituted product **9b** is halogenated by contact with a suitable halogenating agent in an inert organic solvent. Suitable halogenating agents which can be used include diethylaminosulfur trifluoride, [bis(2-methoxyethyl)amino] sulfur trifluoride, and the like. Suitable inert organic solvents which can be used include dichloromethane, ethyl acetate, THF, and the like. The reaction is typically conducted at low temperatures in the range of

approximately -30°C to -78°C. The reaction mixture is gradually allowed to warm to rt and stirred at rt until completion, typically in 6 to 12 h. The reaction mixture is worked up and can be purified by chromatography to provide **9c**.

[0115] The product **9c** is then hydrogenated to provide the product **9d**. The hydrogenation is typically performed in a polar organic solvent such as methanol, ethanol, and the like, using 10% palladium on carbon in a Parr bottle. The bottle is purged, and charged with $H_2$ to approximately 40 to 70 psi and shaken until completion, typically approximately 4 to 24 h. The reaction mixture is filtered, e.g., through a celite pad and washed several times with a polar organic solvent, such as methanol. Evaporation of the combined washings and filtrate affords the product **9d**.

[0116] Scheme 10 below illustrates a general synthesis, as described in Shuman, Journal of Organic Chemistry. **1990**, 55, 741-750, of substituted pyridine carboxylic acid intermediates **10b**, wherein $R^9$ is as defined for formula (I).




**10a** **10b**

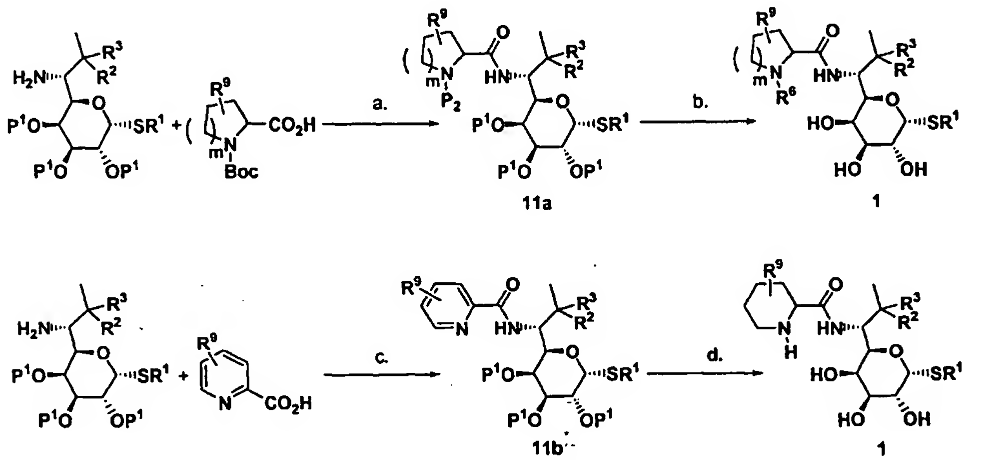
**Scheme 10.** General synthesis of substituted pyridin-2-yl carboxylic acids **10b**.

[0117] As shown in Scheme 10, an appropriately substituted pyridine, is contacted with a suitable oxidizing agent in an inert organic solvent. The appropriately substituted pyridine starting materials are commercially available from vendors such as Aldrich and Sigma. Alternatively, these pyridines can be prepared by methods well known in the art. Suitable oxidizing agents which can be used include hydrogen peroxide, MCPBA, and the like. The reaction is typically conducted at reflux for 6 to 12 h. The reaction mixture is then contacted with a suitable cyanide reagent to provide the cyano-substituted pyridine, **10a**. Suitable cyanide reagents which can be used include trimethylsilyl cyanide, HCN, and the like. Suitable inert organic solvents include dichloromethane, dioxane, THF, and the like. The reaction conveniently can be conducted at rt in approximately 6 to 12 h. The reaction mixture is worked up to provide the cyano-substituted pyridine, **10a**.

[0118] The cyano-substituted pyridine, **10a**, is then hydrolyzed to provide the pyridin-2-yl carboxylic acid **10b** by contact with a suitable acid. Suitable acids for hydrolyzing the cyano

group to the carboxylic acid include hydrochloric acid, aqueous sulfuric acid, and the like. The reaction is typically conducted at reflux in 6 to 12 h.

[0119] Scheme 11 below illustrates the coupling reaction of a lincosamine intermediate, prepared as described above in Schemes 1-5, and a pyrrolidinyl or piperidinyl carboxylic acid, prepared as described above in Schemes 6-10, wherein $R^1$, $R^2$, $R^3$, $R^6$, and $R^9$ are as defined for formula (I) and $P^1$ is a suitable O-protecting group and $P^2$ is a suitable N-protecting group.



**Scheme 11.** General coupling and deprotection methods.

[0120] As shown in Scheme 11, an appropriately 7-substititued lincosamine intermediate (prepared, for example, according to any one of Schemes 1-5) and an appropriately substituted pyrrolidinyl or piperidyl carboxylic acid (prepared, for example, according to any one of Schemes 6-10) are condensed under reactive conditions, preferably in an inert organic solvent, in the presence of a coupling reagent and an organic base. This reaction can be performed with any number of known coupling reagents, such as O-(7-azabenzotriazol-1-yl)-N,N,N',N'tetramethyluronium hexafluorophosphate (HATU), 1-hydroxybenzotriazole hydrate (HOBT) with carbodiimides, diphenylphosphoryl azide (DPPA), isobutyl chloroformate, and the like. Suitable organic bases include diisopropylethylamine (DIEA), triethylamine (TEA), pyridine, N-methyl morpholine, and the like. Suitable inert organic solvents which can be used include, for example, N,N-dimethylformamide, acetonitrile, dichloromethane, and the like. This reaction is typically conducted using an excess of carboxylic acid to lincosamine at temperatures in the range of about 0°C to about 50°C. The reaction is continued until completion, which typically occurs in from about 2 to 12 h.

[0121] Removal of the protecting groups can be carried out with acids, such as trifluoroacetic acid (TFA), hydrochloric acid, p-toluenesulfonic acid, and the like, in an inert

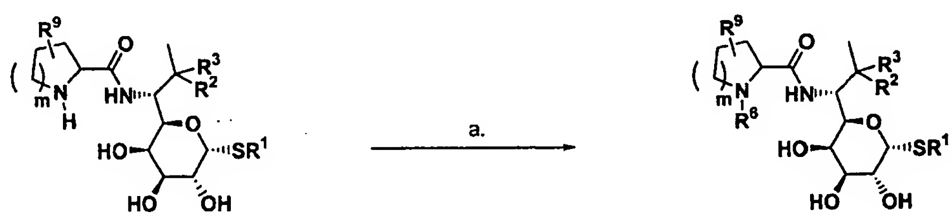
organic solvent such as dichloromethane, dichloroethane, dioxane, THF, and the like. The removal is typically conducted at low temperatures, e.g., 0°C, and then gradually allowed to warm to room temperature to provide the product.

[0122] Also as shown in Scheme 11, an appropriately 7-substitituted lincosamine intermediate (prepared, for example, according to any one of Schemes 1-5) and an appropriately substituted pyridin-2-yl carboxylic acid (prepared, for example, according to Scheme 10) are condensed under reactive conditions, preferably in an inert organic solvent, in the presence of a coupling reagent and an organic base, as described above.

[0123] The pyridine **11b** is hydrogenated to provide the piperidyl product. The hydrogenation is typically performed in a polar organic solvent such as methanol, ethanol, and the like, using platinum(IV)oxide in the presence of an acid such as HCl, acetic acid, and the like, in a Parr bottle. The bottle- is purged, and charged with $H_2$ to approximately 40 to 70 psi and shaken until completion, typically approximately 24 h. The reaction mixture is filtered, e.g., through a celite pad, and washed several times with a polar organic solvent such as methanol. Evaporation of the combined washings and filtrate affords the piperidyl product.

[0124] The coupling of pyridine carboxylic acids and lincosamines to pyridine **11b** followed by reduction to the piperidyl product may also be conducted as described in Birkenmeyer, et al., Journal of Medicinal Chemistry **1984**, 27, 216-223.

[0125] Scheme 12 below illustrates the alkylation of the nitrogen of the pyrrolidinyl or piperidinyl ring, wherein $R^6$ is alkyl, hydroxyalkyl, alkylene-substituted heterocycle, or alkylene-heterocycle, and $R^1$, $R^2$, $R^3$, and $R^9$ are as defined for formula (I).



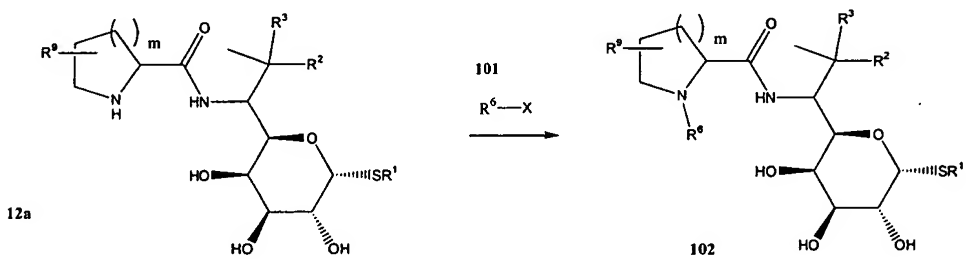

12a 12b

**Scheme 12.** General synthesis of 1'-N-substituted lincosamines. a. alkylating agents

[0126] As shown in Scheme 12, the lincosamine **12a** can be N-substituted by contact with an alkylating agent in the presence of a suitable base to provide a product **12b**. Suitable alkylating agents which can be used include epoxides, alkyl bromides, and the like. Suitable bases which can be used include potassium carbonate, cesium carbonate triethylamine, and the like. The

alkylation reaction is typically conducted in a polar organic solvent such as methanol or DMF. The alkylation reaction is typically conducted at low temperatures in the range of 0°C to -10°C for 10 to 20 h.

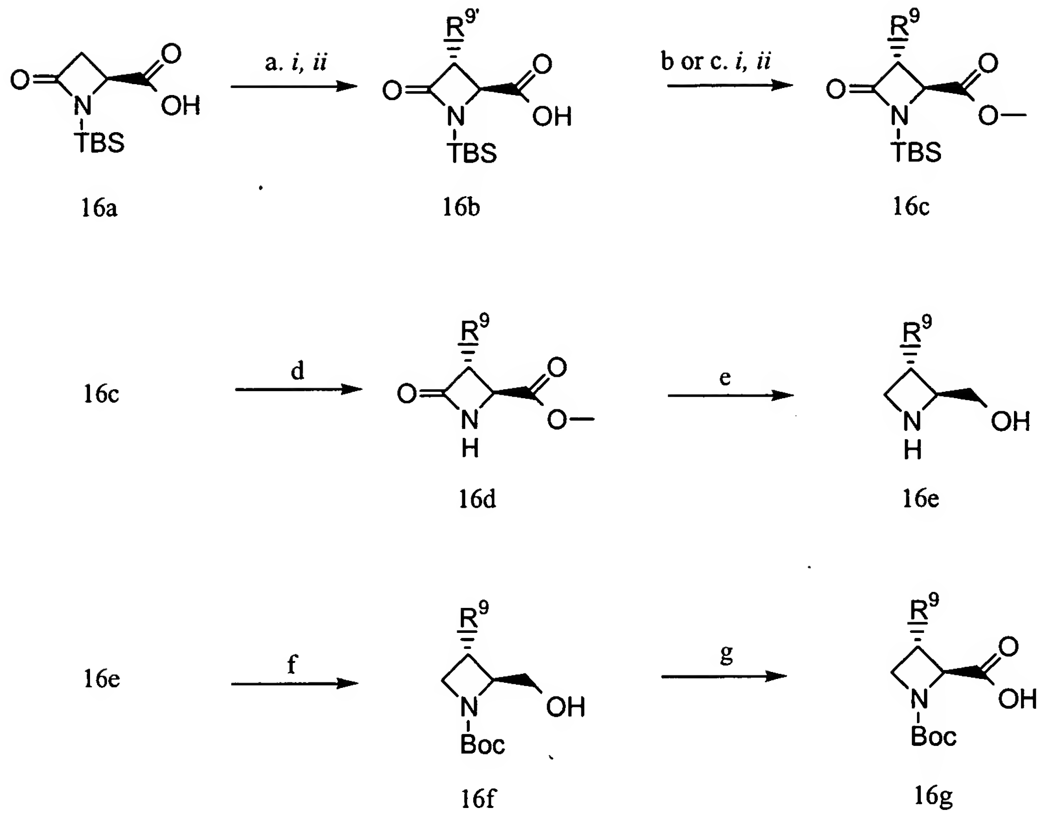
[0127] Scheme 13 below illustrates the acylation of the nitrogen of the pyrrolidinyl or piperidinyl ring, wherein $R^6$ is -C(O)O-alkylene-cycloalkyl, -C(O)O-alkylene-substituted cycloalkyl, -C(O)O-alkyl, -C(O)O-substituted alkyl, -C(O)O-aryl, -C(O)O-substituted aryl, -C(O)O-heteroaryl, -C(O)O-substituted heteroaryl, -[C(O)O]-alkylene-heterocycle, -[C(O)O]-alkylene-substituted heterocycle, and $R^1$, $R^2$, $R^3$, and $R^9$ are as defined for formula (I):




**Scheme 13.** General synthesis of 1'-N-substituted lincosamines.

[0128] As shown in Scheme 13, the lincosamine **12a** can be N-substituted by contact with an acyl chloride **101**, such as $R^6$-X, wherein X is a suitable leaving group, and is preferably halogen, even more preferably chloride in the presence of a suitable base to provide a product **102**. Examples of compound **101**, include bromofluorenyl, Cl-C(O)O-alkyl, Cl-C(O)O-aryl, and the like. Suitable bases which can be used include DCC, TEA, and the like. The reaction is typically conducted in a polar organic solvent such as methanol or DMF. The reaction is typically conducted at low temperatures in the range of -10°C to 20°C.

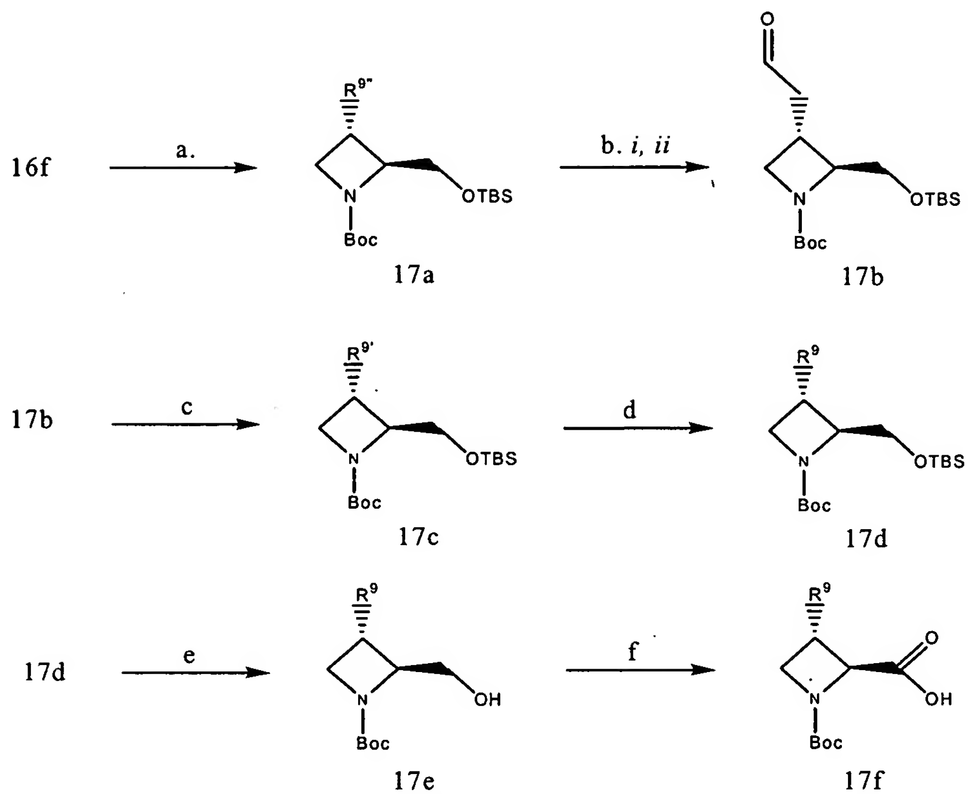
[0129] Scheme 16 below illustrates the general synthesis of *trans*-alkylazetidine carboxylic acids.



Scheme 16. General synthesis of *trans*-alkylazetidine carboxylic acids.

[0130] The following reaction scheme may be used in the synthesis of *trans*-alkylazetidine carboxylic acids, wherein $R^9$ is as defined herein: (a) (i) LDA, THF, 0 °C, (ii) bromoalkane or bromoalkene; (b) $TMSCHN_2$, MeOH, 23 °C; (c) (i) $TMSCHN_2$, MeOH, 23 °C, (ii) $H_2$, Pd/C, EtOAc, 23 °C; (d) $Et_3N.3HF$, THF, 23 °C; (e) $LiAlH_4$, THF, 68 °C; (f) $Boc_2O$, $CH_2Cl_2$, 23°C; (g) $RuCl_3.xH_2O$, $NaIO_4$, acetone, $H_2O$, 23 °C.

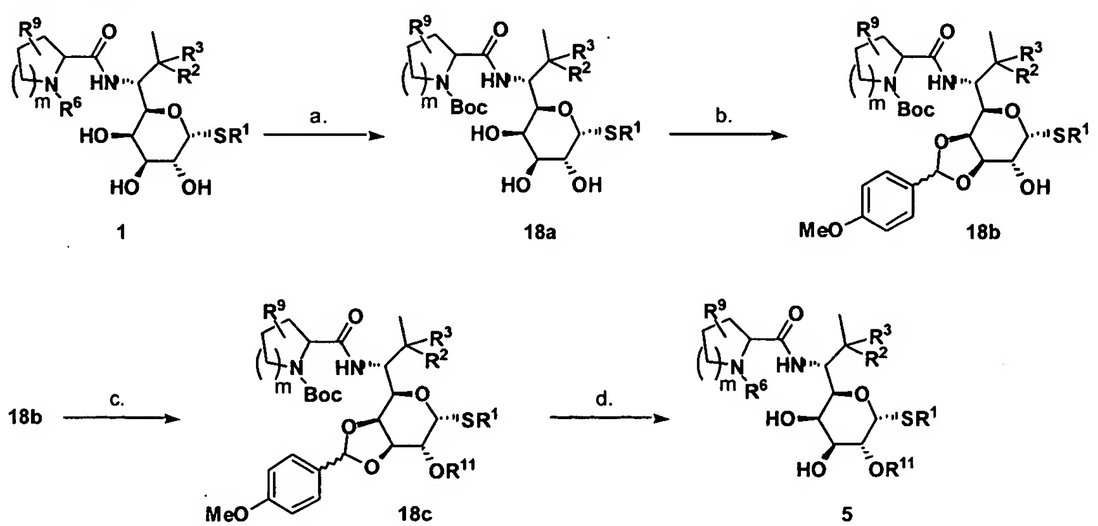
[0131] Scheme 17 below illustrates the general synthesis of trans-alkylazetidine carboxylic acids via the aldehyde.




**Scheme 17.** General synthesis of *trans*-alkylazetidine carboxylic acids via aldehyde.

**[0132]** The following reaction scheme may be used in the synthesis of *trans*-alkylazetidine carboxylic acids: (a) TBSCl, imidazole, DMF, 23 °C; (b) (i) ozone, $CH_2Cl_2$, –78 °C, (ii) $PPh_3$; (c) olefination: $P^+Ph_3$ salt, base, solvent; (d) $H_2$, Pd/C, EtOAc, 23 °C or $KO_2CN{=}NCO_2K$, AcOH, dioxane, 23 °C; (e) TBAF, THF, 23 °C; (f) $RuCl_3.xH_2O$, $NaIO_4$, acetone, $H_2O$, 23 °C.

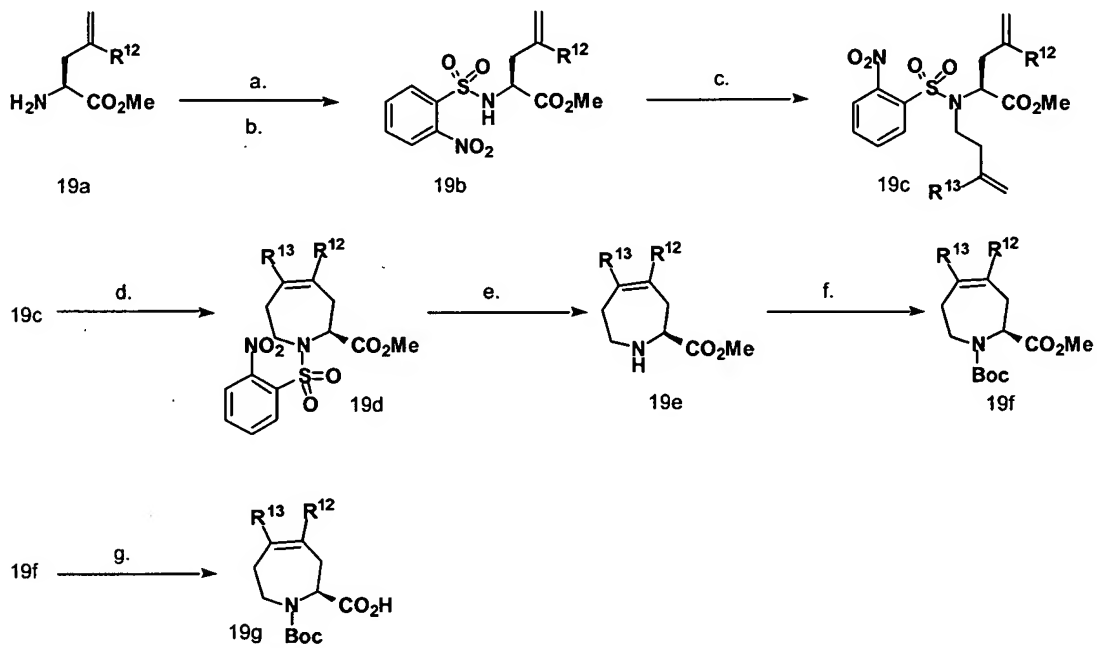
**[0133]** Scheme 18 below illustrates a general synthesis of 2-substituted ester prodrug compounds.



**Scheme 18.** General synthesis of 2-substituted esters.

[0134] The following representative reaction scheme may be used in the synthesis of 2-substituted prodrug compounds of the invention: a. $(Boc)_2O$, aq. $KHCO_3$ THF b. *p*-anisaldehyde dimethyl acetal, PPTS, c. $R^{11}$acylating agent, base d. TFA, DCE, water.

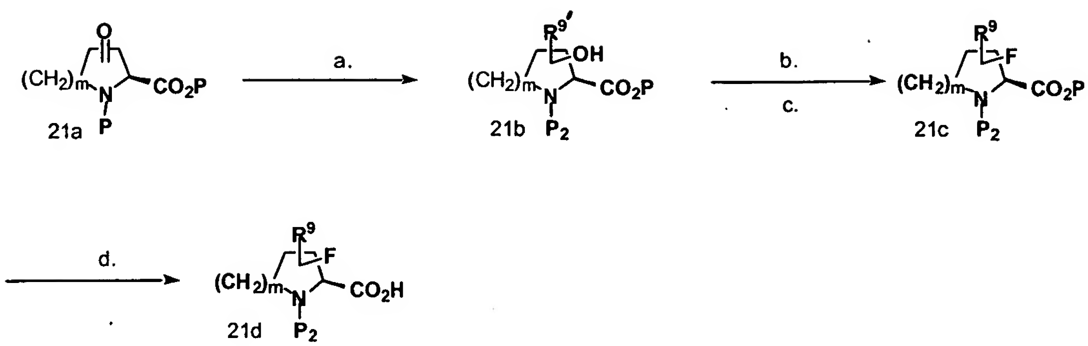
[0135] Scheme 19 below illustrates a general method for the synthesis of 4,5-disubstituted-2,3,6,7-tetrahydro-azepine-2-carboxylic acid derivatives.



**Scheme 19.**

[0136] The following general reaction scheme may be used in the preparation of 4,5-disubstituted-2,3,6,7-tetrahydro-azepine-2-carboxylic acid derivatives: a. 2,2-dimethoxypropane, Catalytic HCl, MeOH b. 2-nitrobenzenesulfonyl chloride, 2,4,6-collidine, dichloroethane c. $Cs_2CO_3$, TBABr, DMF, Homoallylic tosylates or halides d. Benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene] dichloro-(tricyclohexylphosphine)ruthenium e. 7-methyl,1,5,7-triazabicyclo[4.4.0]dec-5-ene, thiophenol f. $(Boc)_2O$, TEA g. Aq. LiOH, Dioxane.

[0137] Scheme 21 below illustrates the synthesis of 4,4 di-substituted pyrrolidine and piperidine carboxylic acids, wherein $R^9$ is a suitable substituent and the other substituent is fluorine.



**Scheme 21.** Synthesis of intermediate **21d** where $R^9$ is defined herein.

[0138] The following representative reaction scheme may be used in Scheme 21: (a) Tetraallyltin, $BF_3 \cdot Et_2O$ or $R^9M$ ($R^9$ or $R^{9'}$ carbon nucleophile) (b) $H_2/Pd$ (c) DAST (d) aq. LiOH or appropriate carboxylate ester deprotection conditions.

Pharmaceutical Formulations

[0139] When employed as pharmaceuticals, the compounds of the subject invention are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, parenteral, transdermal, topical, rectal, and intranasal. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

[0140] This invention also includes pharmaceutical compositions that contain, as the active ingredient, one or more of the compounds of the subject invention above associated with pharmaceutically acceptable carriers. In making the compositions of this invention, the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. The excipient employed is typically an excipient suitable for administration to human subjects or other mammals. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

[0141] In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active

compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g., about 40 mesh.

[0142] Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

[0143] The quantity of active component, that is the compound according to the subject invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application, the potency of the particular compound and the desired concentration.

[0144] The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Preferably, the compound of the subject invention above is employed at no more than about 20 weight percent of the pharmaceutical composition, more preferably no more than about 15 weight percent, with the balance being pharmaceutically inert carrier(s).

[0145] The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically or therapeutically effective amount. It will be understood, however, that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the severity of the bacterial infection being treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[0146] In therapeutic use for treating, or combating, bacterial infections in warm-blooded animals, the compounds or pharmaceutical compositions thereof will be administered orally, topically, transdermally, and/or parenterally at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the animal undergoing treatment which will be antibacterially effective. Generally, such antibacterially or therapeutically effective amount of dosage of active component (i.e., an effective dosage) will be in the range of about 0.1 to about 100, more preferably about 1.0 to about 50 mg/kg of body weight/day.

[0147] For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

[0148] The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

[0149] The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as corn oil, cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

[0150] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable

solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

[0151] The following formulation examples illustrate representative pharmaceutical compositions of the present invention.

**Formulation Example 1**

[0152] Hard gelatin capsules containing the following ingredients are prepared:

| Ingredient | Quantity (mg/capsule) |
|---|---|
| Active Ingredient | 30.0 |
| Starch | 305.0 |
| Magnesium stearate | 5.0 |

[0153] The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

**Formulation Example 2**

[0154] A tablet formula is prepared using the ingredients below:

| Ingredient | Quantity (mg/capsule) |
|---|---|
| Active Ingredient | 25.0 |
| Cellulose, microcrystalline | 200.0 |
| Colloidal silicon dioxide | 10.0 |
| Stearic acid | 5.0 |

[0155] The components are blended and compressed to form tablets, each weighing 240 mg.

**Formulation Example 3**

[0156] A dry powder inhaler formulation is prepared containing the following components:

| Ingredient | Weight % |
|---|---|
| Active Ingredient | 5 |
| Lactose | 95 |

[0157] The active ingredient is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

**Formulation Example 4**

[0158] Tablets, each containing 30 mg of active ingredient, are prepared as follows

| Ingredient | Quantity (mg/capsule) |
|---|---|
| Active Ingredient | 30.0 mg |
| Starch | 45.0 mg |
| Microcrystalline cellulose | 35.0 mg |
| Polyvinylpyrrolidone (as 10% solution in sterile water) | 4.0 mg |
| Sodium carboxymethyl starch | 4.5 mg |
| Magnesium stearate | 0.5 mg |
| Talc | 1.0 mg |
| Total | 120 mg |

[0159] The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50°C to 60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 120 mg.

**Formulation Example 5**

[0160] Capsules, each containing 40 mg of medicament are made as follows:

| Ingredient | Quantity (mg/capsule) |
|---|---|
| Active Ingredient | 40.0 mg |
| Starch | 109.0 mg |
| Magnesium stearate | 1.0 mg |
| Total | 150.0 mg |

[0161] The active ingredient, starch and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

**Formulation Example 6**

[0162] Suppositories, each containing 25 mg of active ingredient are made as follows:

| Ingredient | Amount |
|---|---|
| Active Ingredient | 25 |
| Saturated fatty acid glycerides to | 2,000 mg |

[0163] The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

**Formulation Example 7**

[0164] Suspensions, each containing 50 mg of medicament per 5.0 mL dose are made as follows:

| Ingredient | Amount |
|---|---|
| Active Ingredient | 50 mg |
| Xanthan gum | 4.0 mg |
| Sodium carboxymethyl cellulose (11%) | |
| Microcrystalline cellulose (89%) | 50.0 mg |
| Sucrose | 1.75 g |
| Sodium benzoate | 10.0 mg |
| Flavor and Color | q.v. |
| Purified water to | 5.0 mL |

[0165] The active ingredient, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

**Formulation Example 8**

| Ingredient | Quantity (mg/capsule) |
|---|---|
| Active Ingredient | 15.0 mg |
| Starch | 407.0 mg |
| Magnesium stearate | 3.0 mg |
| Total | 425.0 mg |

[0166] The active ingredient, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 425.0 mg quantities.

**Formulation Example 9**

[0167] A subcutaneous formulation may be prepared as follows:

| Ingredient | Quantity |
|---|---|
| Active Ingredient | 5.0 mg |
| Corn Oil | 1.0 mL |

**Formulation Example 10**

[0168] A topical formulation may be prepared as follows:

| Ingredient | Quantity |
|---|---|
| Active Ingredient | 1-10 g |
| Emulsifying Wax | 30 g |
| Liquid Paraffin | 20 g |
| White Soft Paraffin | to 100 g |

[0169] The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

**Formulation Example 11**

[0170] An intravenous formulation may be prepared as follows:

| Ingredient | Quantity |
|---|---|
| Active Ingredient | 250 mg |
| Isotonic saline | 1000 mg |

[0171] Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[0172] Frequently, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system used for the transport of biological factors to specific anatomical regions of the body is described in U.S. Patent 5,011,472 which is herein incorporated by reference.

[0173] Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of

hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

[0174] Other suitable formulations for use in the present invention can be found in Remington's Pharmaceutical Sciences, Mace Publishing Company, Philadelphia, PA, 17th ed. (1985).

[0175] As noted above, the compounds described herein are suitable for use in a variety of drug delivery systems described above. Additionally, in order to enhance the in vivo serum half-life of the administered compound, the compounds may be encapsulated, introduced into the lumen of liposomes, prepared as a colloid, or other conventional techniques may be employed which provide an extended serum half-life of the compounds. A variety of methods are available for preparing liposomes, as described in, e.g., Szoka, et al., U.S. Patent Nos. 4,235,871, 4,501,728 and 4,837,028 each of which is incorporated herein by reference.

[0176] As noted above, the compounds administered to a patient are in the form of pharmaceutical compositions described above. These compositions may be sterilized by conventional sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 and 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

[0177] In general, the compounds of the subject invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the $LD_{50}$ (the dose lethal to 50% of the population) and the $ED_{50}$ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio $LD_{50}/ ED_{50}$. Compounds that exhibit large therapeutic indices are preferred.

[0178] The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the $ED_{50}$ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the

therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range which includes the $IC_{50}$ (the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

Utility

**[0179]** The compounds, prodrugs and pharmaceutically acceptable salts thereof, as defined herein, may have activity against a variety of bacteria, protozoa, fungi, and parasites. By way of example, the compounds, prodrugs and pharmaceutically acceptable salts thereof may be active against gram positive and gram negative bacteria. The compounds, prodrugs and pharmaceutically acceptable salts thereof may be active against a variety of fungi, including fungi from the genus Mucor and Candida, e.g., Mucor racemosus or Candida albicans. The compounds, prodrugs and pharmaceutically acceptable salts thereof may be active against a variety of parasites, including malaria and cyptosporidium parasite.

**[0180]** The compounds of the subject invention exhibit activity against a variety of bacterial infections, including, for example, gram positive infections, gram negative infections, mycobacteria infections, mycoplasma infections, and chlamydia infections.

**[0181]** Since the compounds of the subject invention exhibit potent activities a variety of bacteria, such as gram positive bacteria, the compounds of the present invention are useful antimicrobial agents and may be effective against a number of human and veterinary pathogens, including gram positive bacteria. The Gram positive organisms against which the compounds of the present invention are effective include Streptococcus pneumoniae, Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis, Enterococcus faecium, Haemophilus influenzae, Moraxella catarrhalis, Escherichia coli, Bacteroides fragilis, Bacteroides thetaiotaomicron, and Clostridium difficile, and the like.

**[0182]** The compounds of the subject invention may be combined with one or more additional antibacterial agents. One or more of the additional antibacterial agents may be active against gram negative bacteria. Additionally, one or more of the additional antibacterial agents may be active against gram positive bacteria. The combination of the compounds of the subject invention and the one or may additional antibacterial agents may be used to treat a gram negative infection. Additionally, the combination of the compounds of the subject invention and

the one or more additional antibacterial agents may be used to treat a gram positive infection. The combination of compounds of the subject invention and the one or more additional antibacterial agents may also be used to treat a mycobacteria infection, mycoplasma infection, or chlamydia infection.

**[0183]** The in vitro activity of compounds of the subject invention may be assessed by standard testing procedures such as the determination of minimum inhibitory concentration (MIC) by agar dilution as described in "Approved Standard. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically," 3rd ed., published 1993 by the National Committee for Clinical Laboratory standards, Villanova, Pennsylvania, USA.

**[0184]** The amount administered to the mammalian patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions are administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. An amount adequate to accomplish this is defined as "therapeutically effective dose." Amounts effective for this use will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the inflammation, the age, weight and general condition of the patient, and the like.

**[0185]** The compositions administered to a patient are in the form of pharmaceutical compositions described above. These compositions may be sterilized by conventional sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

**[0186]** The therapeutic dosage of the compounds of the present invention will vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. For example, for intravenous administration, the dose will typically be in the range of about 20 mg to about 500 mg per kilogram body weight, preferably about 100 mg to about 300 mg per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.1 mg to 1 mg per kilogram body weight. Effective doses

can be extrapolated from dose-response curves derived from in vitro or animal model test systems.

**[0187]** The following synthetic and biological examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention.

## EXAMPLES

**[0188]** In the discussion above and in the examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

| | | |
|---|---|---|
| 7-methyl/MTL | = | 1-methylthio-7-deoxy-7-methyllincosamine |
| apt | = | apparent triplet |
| atm | = | atmospheres |
| Bn | = | benzyl |
| Boc | = | tert-butoxycarbonyl protecting group |
| br s | = | broad singlet |
| BSTFA | = | N,O-bis(trimethylsilyl)trifluoroacetamide |
| Cbz | = | carbonyloxybenzyloxy protecting group |
| $CDCl_3$ | = | deuterated chloroform |
| $CD_3OD$ | = | deuterated methanol |
| cfu | = | colony forming units |
| D | = | doublet |
| DAST | = | dimethylaminosulfurtrifluoride |
| dd | = | doublet of doublets |
| dddd | = | doublet of doublets of doublet of doublets |
| dt | = | doublet of triplets |
| DCC | = | dicyclohexylcarbodiimide |
| DCE | = | dicholoroethane |
| DCM | = | dichloromethane |
| DIEA | = | diisopropyethylamine |
| DMAP | = | dimethylaminopyridine |
| DMF | = | dimethylformamide |
| DMSO | = | dimethyl sulfoxide |
| DPPA | = | diphenylphosphoryl azide |
| $ED_{50}$ | = | dose therapeutically effective in 50% of the population |
| EDC | = | 1-(3-dimethylaminopropyl)-3-ethylcarbodiamide HCl |
| Equiv | = | equivalents |
| ESMS | = | electrospray mass spectrometry |
| Et | = | ethyl |
| EtOAc | = | ethyl acetate |
| $Et_2O$ | = | diethyl ether |
| g | = | grams |
| h | = | hours |
| HATU | = | O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate |
| HBTU | = | O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate |
| HOBT | = | 1-hydroxybenzotriazole hydrate |
| $^1H$ NMR | = | Hydrogen Nuclear Magnetic Resonance spectroscopy |
| HPLC | = | high pressure liquid chromatography |
| Hz | = | hertz |

| | | |
|---|---|---|
| $IC_{50}$ | = | concentration of the test compound which achieves a half-maximal inhibition of symptoms |
| J | = | coupling constant in hertz |
| L | = | liters |
| $LD_{50}$ | = | dose lethal to 50% of the population |
| LDA | = | lithium diisopropylamide |
| LiHMDS | = | lithium hexamethyldisilazide |
| $LiN(iPr)_2$ | = | lithium diisopropylnitride |
| m | = | multiplet |
| M | = | molar |
| MCPBA | = | 2-(4-chloro-o-tolyloxy) acetic acid |
| Me | = | methyl |
| MeCN | = | acetonitrile |
| MeOH | = | methanol |
| mg | = | milligrams |
| MHz | = | megahertz |
| Min | = | minutes |
| mL | = | milliliters |
| Mm | = | millimeter |
| mmol | = | millimol |
| MS(ESPOS) | = | mass spectrometry by positive mode electrospray ionization |
| MS(ESNEG) | = | Mass Spectrometry by negative mode electrospray ionization |
| MTL | = | 1-methylthiolincosamine (methyl 6-amino-6,8-dideoxy-l-thio-erythro-β-D-galacto-octopyranoside) |
| N | = | normal |
| NMR | = | nuclear magnetic resonance |
| OBz | = | benzyloxy protecting group |
| OtBu | = | tert-butoxy |
| Pd/C | = | palladium/carbon |
| pg | = | picograms |
| Ph | = | phenyl |
| PPTS | = | pyridinium *p*-toluenesulfonate |
| Pro | = | L-proline |
| psi | = | pounds per square inch |
| PTFE | = | polytetrafluoroethylene |
| q | = | quartet |
| q.v. | = | quantitative |
| $R_f$ | = | Retention factor |
| rt | = | room temperature |
| s | = | singlet |
| sat. | = | saturated |
| t | = | triplet |
| TBAF | = | tetrabutylammonium fluoride |
| TBS | = | tert-butyldimethylsilyl |
| TEA | = | triethylamine |

| | | |
|---|---|---|
| TFA | = | trifluoroacetic acid |
| THF | = | tetrahydrofuran |
| TLC | = | thin layer chromatography |
| TMS | = | trimethylsilyl |
| $\mu$g | = | micrograms |
| $\mu$L | = | microliters |
| $\mu$m | = | micromolar |
| v/v | = | volume by volume |
| w/w | = | weight by weight |

[0189] Additionally, the term "Aldrich" indicates that the compound or reagent used in the following procedures is commercially available from Aldrich Chemical Company, Inc., 1001 West Saint Paul Avenue, Milwaukee, WI 53233 USA; the term "Fluka" indicates that the compound or reagent is commercially available from Fluka Chemical Corp., 980 South 2nd Street, Ronkonkoma NY 11779 USA; the term "Lancaster" indicates that the compound or reagent is commercially available from Lancaster Synthesis, Inc., P.O. Box 100 Windham, NH 03087 USA; the term "Sigma" indicates that the compound or reagent is commercially available from Sigma, P.O. Box 14508, St. Louis MO 63178 USA; the term "Chemservice" indicates that the compound or reagent is commercially available from Chemservice Inc., Westchester, PA, USA; the term "Bachem" indicates that the compound or reagent is commercially available from Bachem Bioscience Inc., 3700 Horizon Drive, Renaissance at Gulph Mills, King of Prussia, PA 19406 USA; the term "Maybridge" indicates that the compound or reagent is commercially available from Maybridge Chemical Co.

[0190] Trevillett, Tintagel, Cornwall PL34 OHW United Kingdom; the term "RSP" indicates that the compound or reagent is commercially available from RSP Amino Acid Analogs, Inc., 106 South St., Hopkinton, MA 01748, USA, and the term "TCI" indicates that the compound or reagent is commercially available from TCI America, 9211 North Harborgate St., Portland, Oregon, 97203, OR, USA; the term "Toronto" indicates that the compound or reagent is commercially available from Toronto Reasearch Chemicals, Inc., 2 Brisbane Rd., New York, ON, Canada M3J2J8; the term "Alfa" indicates that the compound or reagent is commercially available from Johnson Matthey Catalog Company, Inc. 30 Bond Street, Ward Hill, MA 018350747; and the term "Nova Biochem" indicates that the compound or reagent is commercially available from NovaBiochem USA, 10933 North Torrey Pines Road, P.O. Box 12087, La Jolla CA 92039-2087.

[0191] In the examples below, all temperatures are in degrees Celsius (unless otherwise indicated) and the following general procedures are used to prepared the compounds as

indicated. It will be appreciated by one of skill in the art that the following general procedures are meant to be illustrative only and that the methods may be broadened to synthesize other compounds of the subject invention.

General Procedures

**Method A**

**[0192]** Methyl 6-amino-6,8-dideoxy-1-thio-erythro-β-D-galacto-octopyranoside **1a** ($R^1$ = Me) (MTL) was prepared as described by Hoeksema, H. et al., J. Am. Chem. Soc., **1967,** 89, 2448-2452. N-(Benzyloxycarbonyloxy)succinimide (5.8 g 23.1 mmol) and **1a** (5.0 g, 19.7 mmol) were suspended in pyridine (40mL) and stirred under $N_2$ atmosphere 36 h. The reaction mixture was cooled to 0°C and then bis-N,O-trifluoroacetamide (15.7 mL, 59.0 mmol) was added by syringe over 2 min. The reaction mixture was allowed to warm to rt and stirred for 42 h. Toluene (100 mL) was added and the reaction mixture was evaporated to dryness. The residue was taken up in ethyl acetate (400 mL). The organic solution was washed quickly with 10% citric acid (200 mL), $H_2O$ (3 x 100 mL), saturated $NaHCO_3$ (100 mL), and brine (2 x 100 mL), and dried over $Na_2SO_4$ and evaporated to dryness. Chromatography of the crude product on silica 10% EtOAc/Hexanes containing 0.2% TEA after co-evaporation from toluene (100 mL) and cyclohexane (2 x 100 mL) provided the protected product **1b** (P=Cbz, $R^1$=Me) (7.2 g, 54%) as a colorless oil.

**[0193]** $^1$H NMR (300 MHz, $CD_3SOCD_3$) δ 7.34-7.31 (m, 5), 7.05 (d, J= 8.2, 1), 5.19 (d, J= 5.8, 1), 5.01 (d, J= 1.6, 2), 3.99 (apt dt, J= 5.5, 9.3, 9.3, 2), 3.93-3.86 (m, 3), 3.49 (dd, J= 2.5, 9.6, 1), 2.01 (s, 3), 1.03 (d, J= 6.3, 3), 0.10 (s, 9), 0.09 (s, 9), 0.04 (m, 18).

**[0194]** To dimethylsulfoxide (413 μL, 5.82 mmol) in DCM (1.5 mL) cooled to -72°C was added oxalyl chloride 2 M in DCM (1.49 mL, 2.98 mmol) over 1 min. After 25 min the protected product **1b** (1.92 g, 2.84 mmol) in DCM (4.0 mL) was added by cannula. The resulting reaction mixture was stirred for 25 min and then allowed to warm to -50°C (dry ice acetonitrile) and maintained at this temperature for 2 h. To the reaction mixture was added TEA (1.29 mL, 3.30 mmol). After 25 min the reaction mixture was diluted with EtOAc (300 mL). The resulting organic solution was washed quickly with 5% citric acid (300 mL), $H_2O$ (2 x 300 mL), saturated $NaHCO_3$ (100 mL), brine (100 mL) dried over $Na_2SO_4$ and evaporated to dryness with the aid of toluene (100 mL) to provide the product **1c**. The product **1c** (P=Cbz,

$R^1$=Me) was obtained as a colorless crystalline solid (1.60 g, 94%) after co-evaporation with n-pentane and removal of residual solvent under high vacuum.

**[0195]** $^1$H NMR (300 MHz $CDCl_3$) $\delta$ 7.37-7.33 (m, 5), 5.60 (m, 1), 5.21 (d, J = 5.2, 1), 5.17 (d, J= 12.4, 1), 5.08 (d, J= 12.4, 1), 4.74 (m, 1), 4.16-4.12 (m, 2), 3.87 (d, J = 2.2, 1), 3.69 (dd, J= 2.5, 9.3, 1), 2.01 (br s, 3), 1.90 (s, 3), 0.19 (s, 9), 0.16 (s, 9), 0.15 (s, 9).

## Method B

**[0196]** The Boc-protected product **1c** (P=Boc, $R^1$ =Me) may be prepared in general as outlined above. **1a** ($R^1$ = Me) (MTL) (Dried at 50°C high vacuum) (21.8 g, 86 mmol) was suspended in methanol (200 mL) and TEA (26 mL) and was cooled to 0°C on ice. To this mixture di-t-butyldicarbonate (57.0 g, 0.26 mol) was added. The reaction mixture was then stirred overnight at rt. To the reaction mixture was added toluene (100 mL). The solvents were removed to a total volume of 100 mL, leaving a thick suspension to which cyclohexane (300 mL) was added. The resulting solid precipitate was triturated, then filtered and washed with cyclohexane, ether, and pentane and dried to constant weight. The crude Boc-protected product was used without further purification (87%).

**[0197]** TLC $R_f$= 0.75 (10% MeOH/DCM); MS(ESPOS): 354 $[M+H]^+$; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 0.14 (d, J = 6.3, 3),1.43 (s, 9), 2.07 (s, 3), 3.55 (dd, J = 3.3, 10.43, 1), 3.84 -4.08 (m, 3), 4.10-4.15 (m, 2), 5.25 (d, J = 5.5, 1).

**[0198]** To N-Boc-1-methylthiolincosamide (240 mg, 0.68 mmol) in DMF (5 mL, BSTFA (0.52 mL, 2.0 mmol) and triethylamine (0.14 mL, 1.42 mmol) were added at 0°C and then stirred at rt overnight. DMF was removed and the crude product was quickly passed through a silica gel column (pretreated with 2% TEA in ethyl acetate) eluting with 10% ethyl acetate in hexanes **1b** (P=Boc, $R^1$=Me) (350 mg, 95%). To oxalyl chloride (0.16 mL, 0.78 mmol) in dichloromethane (5 mL) at -60°C, dimethylsulfoxide (0.22 mL, 0.78 mmol) was added slowly and then stirred for 15 min. After which, **1b** (370 mg, 0.65 mmol) in DCM (5 mL) was added slowly. The reaction mixture was stirred for 45 min, during which the reaction temperature was raised to -40°C. Triethylamine (0.70 mL, 3.25 mmol) was then added and the stirring continued for an additional 15 min at -40°C. It was then extracted with DCM (100 mL) and washed with 10% citric acid (50 mL). The residue obtained on removal of solvent was then purified on silica gel column using 10% ethyl acetate in hexanes as eluent **1c** (P=Boc, $R^1$=Me) as a colorless oil (289 mg, 78%).

[0199] TLC: $R_f = 0.60$ (10% EtOAc/Hexanes); MS(ESPOS): 590 $[M+Na]^+$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 18), 0.17 (s, 18), 1.40 (s, 9), 1.84 (s, 3), 2.26 (s, 3), 3.63 (dd, J = 2.7, 9.34, 1), 3.82 (d, J = 1.9, 1), 4.01-4.12 (m, 2), 5.15 (d, J = 5.5, 1).

### Method C

[0200] Triphenylphosphonium bromide (3.29 g, 9.2 mmol) and potassium tert-butoxide (715 mg, 6.4 mmol) under $N_2$ atmosphere were suspended in toluene (31 mL) with vigorous stirring. After 4 h protected product **1c** (P=Cbz, $R^1$=Me) (1.4 g, 2.36 mmol) in toluene (20 mL) was added by cannula. The resulting reaction mixture was stirred 2 h and then diluted with EtOAc (250 mL). The resulting organic solution was washed quickly with $H_2O$ (2 x 100 mL), brine (1 x 100 mL) dried over $Na_2SO_4$ and evaporated to dryness. Chromatography of the crude product on silica 6% EtOAc/Hexanes containing 0.2% TEA gave the alkene product **2a** (P=Cbz, $R^1$=Me, $R^2$=$CH_2$) as a colorless oil that crystallized after co-evaporation from toluene and cyclohexane (0.65 g, 46%).

[0201] 1H NMR (300 MHz $CDCl_3$) δ 7.35-7.27 (m, 5), 6.36 (d, J = 7.1, 1), 5.24 (d, J = 5.5, 1), 5.08 (m, 4), 4.34 (m, 1), 4.16 (m, 2), 3.88 (d, J = 2.2, 1), 3.61 (dd, J = 2.2, 9.3, 1), 2.20 (s, 3), 1.79 (s, 3), 0.17-0.13 (m, 27).

[0202] The product **2a** (P=Cbz, $R^1$=Me, $R^2$=CH2) (490 mg, 0.82 mmol) in ethanol (50 mL) was added to 10% palladium on carbon (Degussa wet form 50% w/w water) (700 mg) in a par bottle. The bottle was purged, and charged with $H_2$ to 65 psi and shaken 24 h. The reaction mixture was filtered through celite, rinsed with methanol. The organic solution was transferred to a resin funnel containing dry, washed Dowex 50w-400x $H^+$ form (0.8 g) and shaken for 10 min. After washing the resin with methanol three times and water two times, the saturated product **2b** ($R^1$ =Me, $R^2$=Me) was eluted from the resin by washing with 5% TEA in MeOH (35 mL, x 10 min x 5). The combined filtrate was evaporated to dryness, co-evaporated from EtOH twice and lyophilized from 1:1 MeCN/$H_2O$ to give the product as a colorless powder (198.4 mg 96%).

[0203] $^1H$ NMR (300 MHz, $D_2O$) δ 5.17 (d, J = 5.8, 1), 3.97-3.84 (m, 3), 3.52 (dd, J = 3.0, 10.0, 1), 2.82 (dd, J = 4.4, 8.5, 1), 1.94 (s, 3),1.89-1.81 (m, 1), 0.82 (d, J = 6.9, 3), 0.72 (d, J = 6.9, 3). MS(ESPOS): 252.2 $[M+H]^+$, (ESNEG): 250.4 $[M-H]^-$.

### Method D

[0204] In the alternative when a Boc-protecting group is used, methyltriphenylphosphonium bromide (12 g, 33.6 mmol) and potassium t-butoxide (3g, 26.7 mmol) were taken in THF (70 mL) at 0°C, and stirred at rt for 4 h. Then Boc-protected product **1c** (P=Boc, $R^1$=Me) (4.7 g, 8.2 mmol) in THF (30 mL) was added and stirred at rt for 2 h. After which it was extracted with EtOAc (300 mL), washed with brine (100 mL) and dried over sodium sulfate. The crude alkene product **2a** (P=Boc, $R^1$=Me, $R^2$=$CH_2$) was purified on silica gel column chromatography using 10% EtOAc in Hexane as eluent (4.1 g, 87.6%).

[0205] TLC: $R_f$ = 0.5 (10% of EtOAc in Hexane): $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.24 (m, 2), 5.22 (d, J = 5.7, 1), 4.21 (m, 1), 4.09 (m, 2), 3.87 (d, J = 2.4, 1), 3.60 (dd, J = 2.7, 9.3, 1), 1.99 (s, 3), 1.76 (s, 3); 1.43 (s, 9); MS(ESPOS): 444 (M-2TMS+Na).

[0206] To the product **2a** (P=Boc, $R^1$=Me, $R^2$=$CH_2$) in methanol (30 mL), Dowex $H^+$ resin (1 g) was added and stirred at rt for 1 h. The resin was filtered and the product obtained on removal of solvent (2.4 g, 6.8 mmol,) was taken in MeOH (30 mL). Pd/C (2.5 g) was added and hydrogenated at 55 psi overnight. The crude product obtained on filtering and removal of solvent was purified on silica gel column chromatography using 10% MeOH in DCM to provide Boc-protected 7-Methyl MTL as a white solid (2.06 g, 86%). TLC $R_f$= 0.5 (10% of MeOH in DCM).

[0207] $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 5.23 (d, J = 5.4, 1), 4.11 (m, 1), 3.97 (d, J = 10.2, 1), 3.84 (m, 1), 3.52 (m, 1), 2.08 (s, 3), 1.44 (s, 9), 1.14 (m, 1), 0.93 (d, J = 6.9, 3), 0.85 (d, J = 6.9, 3); MS(ESPOS): 351$[M+H]^+$.

[0208] To the Boc-protected 7-Methyl MTL (150 mg, 0.43 mmol) in dichloroethane (6 mL), dimethylsulfide (0.16 mL, 2.5 mmol) was added, followed by TFA (2 mL), water (0.16 mL) and stirred at rt for 1 h. The solvent was removed to obtain the crude product **2b** ($R^1$=Me, $R^2$=Me). After purification on silica gel column chromatography using 30% MeOH in DCM as eluent, the product **2b** ($R^1$=Me, $R^2$=Me) was obtained identical in all respects to the material obtained from method C.

### Method E

[0209] Sodium hydride (80 mg, 3.3 mmol) under $N_2$ atmosphere was suspended in THF (4 mL) with vigorous stirring. The suspension was cooled to -30°C and diethyl(cyanomethyl)phosphonate (805 $\mu$L, 5.0 mmol) was added. After 30 min protected

product **1c** (P=Cbz, $R^1$=Me) (1.0 g, 1.7 mmol) in THF (3 mL) was added by cannula. The resulting reaction mixture was stirred 4 h and then diluted with EtOAc (250 mL). The resulting organic solution was washed quickly saturated aqueous $NaHCO_3$ (1 x 100 mL), brine (1 x 50 mL) dried over $Na_2SO_4$ and evaporated to dryness. Chromatography of the crude product on silica 6% EtOAc/Hexanes to 10% EtOAc/Hexanes containing 0.2% TEA gave the protected alkene product **2a** (P=Cbz, $R^1$=Me, $R^2$=CHCN) as a colorless oil (0.38 g, 37%). MS(ESPOS): 625.5.2 $[M+H]^+$, ES(NEG): 659.5 [M+Cl].

**[0210]** The product **2a** (P=Cbz, $R^1$=Me, $R^2$=CHCN) (180 mg, 0.29 mmol) in ethanol (15 mL) was added to 10% palladium on carbon (Degussa wet form 50% w/w water) (300 mg) in a Parr bottle and concentrated HCl (29 $\mu$L) was added. The bottle was purged, and charged with $H_2$ to 65 psi and shaken for 24 h. The reaction mixture was filtered through celite, rinsed with methanol. The organic solution was transferred to a resin funnel containing dry, washed Dowex 50w-400x $H^+$ form (1 g) and shaken 10 min. After washing the resin with methanol twice and water, the saturated product **2b** ($R^1$=Me, $R^2$=$CH_2CN$) was eluted from the resin by washing with 5% TEA in MeOH (20 mL x 20 min x 3) and MeCN (20 mL x 20 min). The combined organic filtrate was evaporated to dryness lyophilized from 1:1 MeCN/$H_2O$ to give the product **2b** ($R^1$=Me, $R^2$=$CH_2CN$) as a colorless solid (70 mg, 91%). ES(NEG): 275.3 $[M-H]^-$.

**Method F**

**[0211]** To the protected product **1c** (P=Cbz, $R^1$=Me) (0.75g, 1.3 mmol) in THF (7.3 mL) was added MeMgCl (3M) in THF (7.0 mL 2.1 mmol) at 0°C. Over 30 min the reaction mixture was warmed to 4°C and after 4 h the reaction mixture was quenched with 1:3 saturated aqueous $NH_4Cl/H_2O$ (10mL). The quenched mixture was diluted to 100 mL with water and extracted with DCM (4 x 50 mL). The combined organic phase was dried and evaporated. The residue was dissolved in 1:2:4 $H_2O$/HOAc/THF (100 mL) and stirred for 20 h, and then evaporated with the aid of toluene (2 x 100 mL). Chromatography 10:1 to 10:2 DCM / MeOH gave product **3a** (P=Cbz, $R^1$=Me, $R^2$=Me) (153 mg, 31%).

**[0212]** (ESNEG): 399.5 $[M-H]^-$.

**[0213]** **3a** (P=Cbz, $R^1$=Me, $R^2$=Me) (79 mg, 0.2 mmol) in ethanol (10 mL) was added to 10% palladium on carbon (Degussa wet form 50% w/w water) (400 mg) in a Parr bottle. The bottle was purged, and charged with $H_2$ to 65 psi and shaken 6 h. The reaction mixture was filtered through celite, rinsed with methanol. The combined filtrate was evaporated to dryness

and lyophilized from 1:1 MeCN/$H_2O$ to give the product **3b** ($R^1$=Me, $R^2$=Me) as a colorless powder (42 mg, 80%).

**[0214]** $^1$H NMR (300 MHz, $D_2O$) $\delta$ 5.33 (d, J = 5.8,-l), 4.83-4.06 (m, 3), 3.65-3.60 (m, 1), 3.06-3.03 (m, 1), 2.18 (s, 3), 1.30 (s, 3), 1.23 (s, 3). MS(ESPOS): 268.4 $[M+H]^+$, MS(ESNEG): 266.2 $[M-H]^-$.

**Method G**

**[0215]** To the Boc-protected product **1c** (P=Boc, $R^1$=Me) (100 mg, 0.18 mmol) in methanol (3 mL), O-trimethylsilylhydroxylamine (0.10 mL, 0.88 mmol) was added and stirred at rt overnight. The solvent was removed to obtain the crude Boc-protected product **4a** (P=Boc, $R^1$=Me, $R^7$=H). To the crude product **4a** (95 mg, 0.15 mmol), 30% trifluoroacetic acid in dichloroethane (10 mL) and dimethyl sulfide (0.5 mL) were added and stirred for 1 h. The solvent was removed and the product **4b** ($R^1$=Me, $R^7$=H) was taken as such for the next step.

**[0216]** TLC: $R_f$= 0.35 (10% MeOH/DCM); MS(ESPOS): 267 $[M+H]^+$; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 1.96 (s, 3), 2.09 (s, 3), 3.58 (dd, J = 3.3, 10.2, 1), 3.90 (s, 1), 4.11 (dd, J = 5.7, 10.20, 1), 4.19 (d, J = 5.4, 1), 4.50 (d, J = 5.1, 1), 5.36 (d, J = 5.7, 1).

**Method H**

**[0217]** To the Boc-protected product **1c** (P=Boc, $R^1$=Me) (100 mg, 0.176 mmol) in methanol (4 mL) and water (1 mL), O-alkylhydroxylamine hydrochloride (for example, O-methylhydroxylamine hydrochloride) (60 mg, 0.70 mmol) and sodium acetate (57 mg, 0.70 mmol) were added and heated at 80°C for 3 h and then stirred at rt overnight. The solvent was removed under high vacuum to obtain the crude Boc-protected product **4a** (P=Boc, $R^1$=H, $R^7$=Me). The crude product **4a** was taken in 30% trifluoroacetic acid in dichloroethane (10 mL), dimethylsulfide (0.5 mL) and stirred for 1 h at rt. The solvent was removed and the residue was kept under high vacuum for 1 h and the product **4b** ($R^1$=Me, $R^7$=Me) was taken as such for the next step.

**[0218]** TLC: $R_f$= 0.63 (10% MeOH/DCM); MS(ESPOS): 281 $[M+H]^+$. $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 1.95 (s, 3), 2.08 (s, 3), 3.60 (dd, J = 3.3, 10.20, 1), 3.92 (s, 3), 4.13 (dd, J = 4.8, 10.20, 1), 4.49 (d, J = 1.2, 1), 5.38 (d, J = 5.4, 1).

## Method I

[0219] To the Boc-protected product **1c** (P=Boc, $R^1$=Me) (500 mg, 0.88 mmol) in THF (10 mL), tetrabutylammonium fluoride (2.5 mmol, 1 M in THF) was added and the reaction mixture was stirred at rt for 1 h. The solvent was removed and the residue was purified on silica gel column using 5% methanol in dichloromethane as eluent. The product (111 mg, 0.31 mmol) obtained from the column was then taken in a mixture of dichloromethane (3 mL) and pyridine (3 mL) to which acetic anhydride (0.5 mL, 10.6 mmol) and dimethylaminopyridine (80 mg, 1.7 mmol) were added and stirred at rt overnight. The solvent was removed and the crude product was purified on silica gel column using 30% ethyl acetate in hexanes as eluent to provide **5a** (P=Boc, $R^1$=Me) (58 mg, 38%).

[0220] TLC: $R_f$ = 0.73 (50% EtOAc/Hexanes); MS(ESPOS): 500 $[M+Na]^+$. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.38 (s, 9), 1.91 (s, 3), 1.98 (s, 3), 2.07 (s, 3), 2.18 (s, 3), 4.33 (m, 1), 4.72 (m, 1), 4.94 (m, 1), 5.21 (m, 2), 5.45 (s, 1), 5.57 (m, 1).

[0221] To product **5a** (P=Boc, $R^1$=Me) (158 mg, 0.331 mmol) in DCM (5 mL), dimethylaminosulfurtrifluoride (732 $\mu$L, 3.31 mmol) was added and stirred overnight. More DCM was added and the organic portion was washed with sodium bicarbonate. The residue obtained on removal of solvent was purified on silica gel column chromatography using 20% ethyl acetate in hexanes as eluent (100 mg, 60%) to provide the protected product (P=Boc, $R^1$=Me). The Boc-protected product was taken up in 30% trifluoroacetic acid in dichloroethane and dimethylsulfide and stirred for 1 h at rt. The solvent was removed to provide the product **5b** ($R^1$=Me).

[0222] TLC: $R_f$ = 0.63 (40% MeOH/Hexanes); MS(ESPOS): 522 $[M+Na]^+$. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.40 (s, 9), 1.69 (t, J = 18.9, 3), 1.98 (s, 3), 2.08 (s, 6), 2.13 (s, 3), 4.22-4.30 (m, 1), 4.53 (dd, J = 10.9, 25.3, 1), 5.16-5.28 (m, 2), 5.52 (s, 1), 5.63 (d, J = 5.2, 1).

## Method J

[0223] Enolization (LiHMDS) and alkylation of **7a** with 4-bromo-2-methyl-2-butenyl afforded a mixture of diastereomers of the lactam **7b** ($R^{9'}$=2-methyl-2-butenyl) (61%) according to the literature procedure by Zhang, R.; et al., Journal of the American Chemical Society. **1998**, 120, 3894-3902. Compound **7a** is commercially available from vendors such as Bachem. Alternatively, **7a** can be prepared by methods well known in the art for an example see Baldwin, et al.; Tetrahedron, **1989**, 45, 7449-7468.

[0224] The lactam **7b** was reduced to the pyrrolidine **7c** ($R^{9'}$=2-methyl-2-butenyl) (70%) by the two-step sequence involving superhydride reduction of the lactam to the hemiaminal and the subsequent reduction of the hemiaminal with $Et_3SiH/BF_3{\bullet}OEt_2$. The pyrrolidine **7c** ($R^{9'}$=2-methyl-2-butenyl) (778 mg, 2.08 mmol), 10% palladium on carbon (230 mg), in anhydrous methanol (25 mL) was subjected to Parr hydrogenolysis at 50 psi for 5 h. The reaction mixture was filtered through a celite pad and washed several times with methanol. The combined washings and filtrate were evaporated to dryness, affording, without further purification, a colorless oil **7d** ($R^9$=2-methylbutyl).

[0225] TLC: $R_f$= 0.3 [Solvent system: DCM:hexanes:MeOH(6:5:1)]. MS(NEGATIVE): 284.5 $[M-H]^-$.

## Method K

[0226] Enolization (LiHMDS, 33 mmol, 33 mL, 1.1 equiv) and alkylation of **7a** (9.47 g, 29.7 mmol, 1 equiv) with cis-1-bromo-2-pentene (4.21 mL, 35.6 mmol, 1.2 equiv), in anhydrous THF at -78°C under nitrogen, afforded a mixture of diastereomers of the lactam **7b** ($R^{9'}$=2-pentenyl) (43.2%) after silica gel purification. The lactam **7b** (3.96g, 10.22mmol) was reduced to the pyrrolidine **7c** ($R^{9'}$=2-pentenyl) by the two-step sequence involving superhydride reduction of the lactam to the hemiaminal, at -78°C in anhydrous THF, and the subsequent reduction of the hemiaminal with $Et_3SiH/BF_3OEt_2$ in anhydrous DCM at -78°C affording **7c** ($R^{9'}$=2-pentenyl) (71%) after silica gel purification. The pyrrolidine **7c** (2.71 g, 7.26 mmol), 10% palladium on carbon (560mg), in anhydrous methanol (30 mL) was subjected to Parr hydrogenolysis at 50 psi for 5 h. The reaction mixture was filtered through a celite pad and washed several times with methanol. The combined washings and filtrate were evaporated to dryness, affording, without further purification, a colorless oil **7d** ($R^9$=pentyl) (1.68g, 80%).

[0227] TLC: $R_f$= 0.3 [Solvent system:DCM:hexanes:MeOH(6:5:1)]. MS(ESNEG): 284.5 $[M-H]^-$.

## Method L

[0228] Ozonolysis of **7d** ($R^9$=2-methylbutyl) in anhydrous dichloromethane followed by treatment with DMS at -78°C afforded aldehyde **8a** (77%). 4-Fluorobenzyl phosphonium chloride (0.87 g, 2.13 mmol) and potassium t-butoxide (0.17 g, 1.48 mmol) were suspended in toluene under nitrogen with vigorous stirring. After 4 h, a solution of aldehyde **8a** (204 mg, 0.59

mmol) in toluene (4.6 mL) was added drop-wise. The reaction mixture was stirred at rt for 2 h and diluted with ethyl acetate (50 mL). The organic layer was washed with water (2 x 20 mL), brine, dried and concentrated. The residue was purified by chromatography to give a clear syrup **8b** ($R^{9'}$=3-(4-fluorophenyl)prop-2-enyl) (171 mg).

**[0229]** To a solution of **8b** ($R^{9'}$=3-(4-fluorophenyl)prop-2-enyl) (171 mg, 0.39 mmol) in MeOH (25 mL) in a Parr bottle was added 10% palladium on carbon (Degussa wet form 50% w/w water) (200 mg). The bottle was purged and charged with $H_2$ to 40 psi, and shaken for 4 h. The reaction mixture was filtered through celite and rinsed with MeOH. The filtrate was concentrated to give a yellow oil **8c** ($R^9$=3-(4-fluorophenyl)propyl) (120 mg).

**[0230]** MS(ESPOS): 374.5 $[M+Na]^+$, MS(ESNEG): 350.3 $[M-H]^-$.

**Method M**

**[0231]** 4-Chlorobenzyl phosphonium chloride (0.95g, 2.24 mmol, 3.9 equiv) and potassium t-butoxide (0.17 g, 1.55 mmol, 2.7 equiv) were suspended in toluene (7.5 mL) under nitrogen with vigorous stirring. After 4 h, a solution of aldehyde **8a** (200 mg, 0.58 mmol, 1 equiv) in toluene (4.9 mL) was added dropwise. The reaction mixture was stirred at rt for 2 h and diluted with ethyl acetate (50 mL). The organic layer was washed with water (2 x 20 mL), brine, dried and concentrated. The residue was purified by chromatography to give a clear syrup **8b** ($R^{9'}$=3-(4-chlorophenyl)prop-2-enyl) (216 mg, 82%).

**[0232]** MS(ESPOS): 478.5 $[M+Na]^+$, MS(ESNEG): 454.4 $[M-H]^-$.

**[0233]** To a solution of **8b** ($R^{9'}$=3-(4-chlorophenyl)prop-2-enyl) (147 mg, 0.32 mmol) in cyclohexane (50 mL) was added 10% palladium on carbon (Degussa wet form 50% w/w water) (80 mg). The reaction mixture was stirred at rt under 1 atm $H_2$ overnight. The reaction mixture was filtered through celite and rinsed with MeOH. The filtrate was concentrated to give the alkane product **8c** ($R^9$=3-(4-chlorophenyl)propyl) as a clear oil (131 mg, 89%). To a solution of the alkane (131 mg, 0.29 mmol, 1 equiv) in THF (3 mL) and water (1 mL) was added lithium hydroxide monohydrate (60 mg, 1.43 mmol, 5 equiv). The reaction mixture was stirred at rt overnight. The THF was removed under vacuum. The residue was diluted with water (5 mL) and washed with ether (10 mL). The aqueous layer was taken up in ethyl acetate (60 mL) and partitioned with 10% citric acid (30 mL). The organic layer was washed with water and brine, dried and concentrated to give a clear syrup **8c** ($R^9$=3-(4-chlorophenyl)propyl) (105 mg, 100%).

**[0234]** MS(ESPOS): 390.4 $[M+Na]^+$, 268.4 $[M-Boc+H]^+$.

## Method N

[0235] To a solution of aldehyde **8a** (406.5 mg, 1.17 mmol, 1 equiv) in dimethyl acetamide (0.25 mL) at 0 °C was added dibromodifluoromethane (0.21 mL, 2.34 mmol, 2 equiv). To the stirred mixture was added a solution of triphenylphosphine (0.61 g, 2.34 mmol, 2 equiv) in dimethyl acetamide (0.5 mL) over a period of 20 minutes under nitrogen. The reaction mixture was warmed to rt and stirred for 30 minutes, and then was added to an activated zinc (0.25g, 3.82 mmol, 3.3 equiv) with the aid of dimethyl acetamide (0.3 mL). The resulting reaction mixture was stirred at 110°C for 1 h and cooled to rt and filtered with the aid of dimethylacetamide (7 mL). The filtrate was poured into ice water (100 mL) and extracted with ether (150 mL). The ether layer was washed with brine, dried and concentrated. The residue was purified by chromatography to give a clear oil **8b** ($R^{9'}$=3,3-difluoroprop-2-enyl) (182 mg, 41 %).

[0236] MS(ESPOS): 282.4 $[M - Boc + H]^+$.

[0237] To a solution of **8a** ($R^{9'}$=3,3-difluoroprop-2-enyl) (126 mg, 0.33 mmol) in MeOH (35 mL) was added 10% palladium on carbon (Degussa wet form 50% w/w water) (120 mg). The reaction mixture was stirred at rt under hydrogen (1 atm) overnight and was filtered through celite with the aid of MeOH. The filtrate was concentrated to give a clear syrup **8c** ($R^9$=3,3-difluoropropyl) (97 mg, 100%).

[0238] MS(ESPOS): 194.4 $[M - Boc + H]^+$, MS(ESNEG): 292.4 $[M-H]^-$.

## Method O

[0239] To a solution of aldehyde **8b** (258 mg, 0.74 mmol, 1 equiv) in THF (3 mL) at 0°C was added tetraallyltin (178 $\mu$L, 0.74 mmol, 1 equiv), followed by the drop-wise addition of boron trifluoride etherate (94.3 $\mu$L, 0.74 mmol, 1 equiv) over a period of 15 min. The reaction mixture was stirred at 0°C for 1.5 h. Then a solution of potassium fluoride (125 mg) in water (1.25 mL) was added. The resulting mixture was warmed to rt and stirred at rt for 20 min. This was followed by the addition of methanol (10 mL) and the resulting mixture was stirred at rt for another 20 min. The reaction mixture was filtered over celite. The filtrate was evaporated to dryness. The residue was diluted with dichloromethane (100 mL), washed with water (50 mL), dried, concentrated and purified by chromatography to give a clear oil **9a** ($R^9$=2-hydroxypent-4-enyl) (261 mg, 90%): MS(ESPOS): 412.5 $[M + Na]^+$, 290.4 $[M - Boc + H]^+$.

[0240] To a solution of dimethylsulfoxide (0.17 mL, 2.42 mmol, 3 equiv) in dichloromethane (0.5 mL) at -72°C was added a 2 M solution of oxalyl chloride in dichloromethane (0.61 mL, 1.21 mmol, 1.5 equiv) over a period of 1 min. The mixture was stirred at -72°C for 25 min, followed by the drop-wise addition of a solution of the alcohol **9a** (314 mg, 0.81 mmol, 1 equiv) in dichloromethane (1.4 mL) over a period of 2 min. The reaction mixture was stirred at -72°C for 25 min, then warmed to -50°C and stirred for an additional 2 h. Triethylamine (0.56 mL, 4.04 mmol, 5 equiv) was added and stirred at -50°C for 25 min. The mixture was diluted with ethyl acetate (100 mL), washed with 5% citric acid (100 mL), water, saturated aqueous $NaHCO_3$ and brine, dried, evaporated and coevaporated with anhydrous toluene to give a clear syrup **9b** ($R^9$=2-propenylcarboxymethyl) (287 mg, 92%). MS(ESPOS): 288.5 $[M - Boc + H]^+$; MS(ESNEG): 386.2 $[M-H]^-$.

[0241] To a solution of ketone **9b** (225.1 mg, 0.58 mmol, 1 equiv) in dichloromethane (2 mL) at -78°C was added diethylaminosulfur trifluoride (0.46 mL, 3.49 mL, 6 equiv). The reaction mixture was warmed to rt and stirred at rt for 3 h, followed by an addition of additional (diethylamino)sulfur trifluoride (0.46 mL, 3.49 mL, 6 equiv) at -78°C. The mixture was warmed to rt and stirred overnight. Then the mixture was diluted with dichloromethane (60 mL), washed with sat. aqueous $NaHCO_3$ (1 x), brine (1 x), dried, and evaporated. The residue was purified by chromatography to give a yellow oil **9c** (X, X=fluoro, flouro) (75 mg, 32%).

[0242] MS(ESPOS): 310.5 $[M - Boc + H]^+$.

[0243] To a solution of **9c** ($R^9$=2,2-difluoropent-4-enyl) (85 mg, 0.21 mmol) in MeOH (20 mL) was added 10% palladium on carbon (Degussa wet form 50% w/w water) (100 mg). The reaction mixture was stirred at rt under hydrogen (1 atm) overnight, was filtered through celite with the aid of MeOH (10 mL). To the filtrate was added 10% palladium on carbon (Degussa wet form 50% w/w water) (130 mg). The reaction mixture was stirred at rt under hydrogen (1 atm) overnight, was filtered through celite with the aid of MeOH (10 mL). The filtrate was concentrated to give haloalkyl N-Boc-amino acid **9d** (X,X=fluoro, fluoro) (67.7 mg, 100%) as a clear syrup.

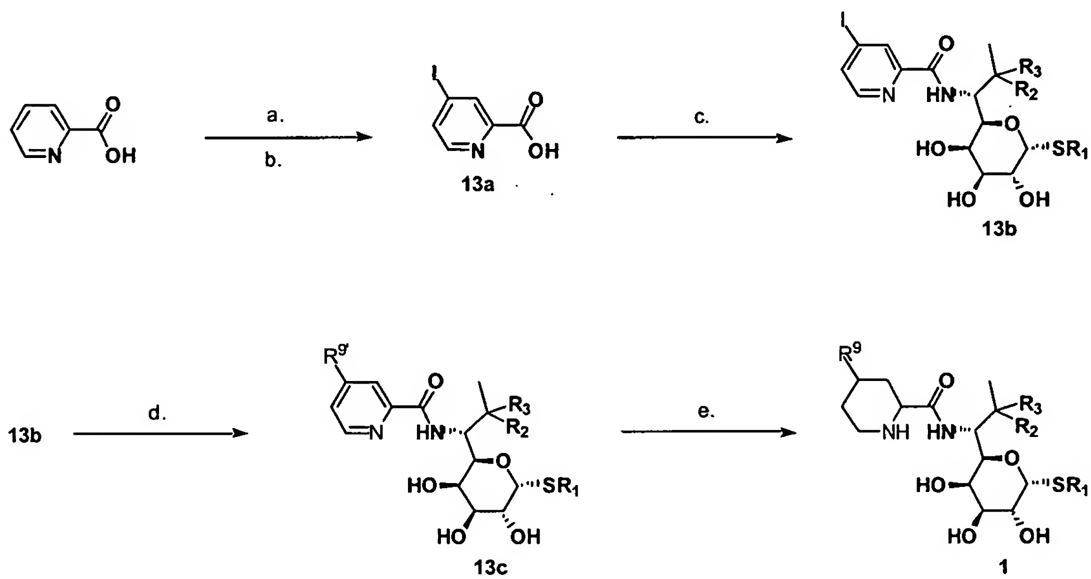
[0244] MS(ESPOS): 344.4 $[M + Na]^+$, 222.4 $[M - Boc + H]^+$ MS(ESNEG): 320.2 $[M-H]^-$.

**Method P**

[0245] To 4-propylpyridine (2.5 g, 20 mmol), 30% hydrogen peroxide (2.4 g) was added and refluxed overnight. The solvent was removed and the resulting residue was taken in DCM (30

mL). Trimethylsilyl cyanide (2.6 g, 26 mmol) was added to the above solution followed by dimethylcarbamyl chloride (2.8 g, 26 mmol), and the reaction mixture was stirred at rt overnight. Potassium carbonate (10%, 100 mL) was added. The organic layer was separated, dried over sodium sulfate and then concentrated to obtain 4-propyl-2-cyanopyridine (2.5 g, 93%). It was then refluxed in hydrochloric acid (6N, 60 mL) for overnight. The 4-propyl-2-carboxylic acid pyridine **10b** ($R^9$=propyl) was obtained after crystallization from acetonitrile (2g, 71%).

**[0246]** MS(ESPOS): 166 $[M+H]^+$; $^1H$ NMR (300 $MH_2$, $CD_3OD$) $\delta$ 8.75 (dd, J= 9.0, 3.0, 1), 8.42 (s, 1), 8.08 (dd, J = 9.0, 3.0, 1), 3.00 (t, J = 7.5, 2), 1.82 (m, 2), 1.05 (t, J = 7.2, 3).




## Method Q

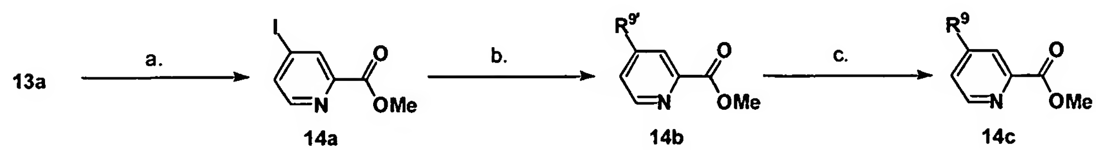
**[0247]** A mixture of picolinic acid (Aldrich) (20 g, 162 mmol, 1 equiv) and sodium bromide (33.43 g, 325 mmol, 2 equiv) in thionyl chloride (81 mL) was refluxed for 5 h. The solvent was removed under vacuum. Absolute methanol (160 mL) was added and the mixture was stirred at rt for 30 minutes. The solvent was evaporated, and the residue was taken up in 5% sodium bicarbonate and extracted with ethyl acetate (3x). The organic layers were combined and dried over $MgSO_4$ and evaporated. The residue was purified by chromatography to give 4-chloropicolinic acid methyl ester as a white solid (19.9 g, 72%): $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.63 (d, J = 5.4, 1), 8.13 (d, J = 2.1, 1), 7.48 (dd, J = 2.0, 5.3, 1), 4.00 (s, 3).

**[0248]** A mixture of 4-chloropicolinic acid methyl ester (2.4 g, 14.1 mmol), 57% hydroiodic acid (13.3 mL) and 50% aqueous hypophosphorous acid (0.66 mL) was stirred at 85 °C for 2 h and then was stirred at 107 °C overnight. The mixture was cooled to 95 °C. At this temperature over 30 minutes 10 M sodium hydroxide aqueous solution (4.2 mL) was added, followed by the addition of water (15.2 mL). The mixture was cooled to rt and stirred at rt for 1h. The precipitate was filtered, washed with cold water and dried under high vacuum overnight to give 4-iodopipecolinic acid **13a** (3.5 g, 66%): $^1$H NMR (300 MHz, DMSO $d_6$) δ 8.39 (d, J = 5.1, 1), 8.35 (d, J = 1.8, 1), 8.07 (dd, J = 1.7, 5.2, 1); MS (ESPOS): 250.2 $[M+H]^+$.

**[0249]** To a mixture of 7-Me MTL HCl salt **2b** ($R^1$=Me, $R^2$=Me) (200 mg, 0.69 mmol, 1 equiv) in dry DMF (1.8 mL) at 0 °C was added triethylamine (0.50 mL, 3.61 mmol, 5.2 equiv), followed by the addition of BSTFA (0.28 mL, 1.04 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C for 10 minutes, and then was stirred at rt for 50 minutes. To the reaction mixture was added the acid **13a** (341 mg, 0.90 mmol, 1.3 equiv) and HATU (423 mg, 1.11 mmol, 1.6 equiv). The reaction mixture was stirred at rt for 3 h. The reaction mixture was evaporated to dryness, taken up in ethyl acetate, washed with water (1 x), sat. $NaHCO_3$ (1 x) and brine. The organic layer was dried over $Na_2SO_4$ and evaporated to give a yellow residue which was dissolved in methanol (20 mL) to which was added dry Dowex resin (250 mg). The reaction mixture was stirred at rt for 1 h. The resin was removed by filtration and the crude product eluted with 2M ammonia in methanol. The methanolic eluent was evaporated, and the resulting residue was purified by chromatography to provide a white solid **13b** ($R^1$=Me, $R^2$= Me, $R^3$=H) (250 mg, 75%): $^1$H NMR (300 MHz, $CD_3OD$) δ 8.46 (d, J = 1.8, 1), 8.30 (d, J = 5.4, 1), 7.98 (dd, J = 1.8, 5.1, 1), 5.25 (d, J = 6.0, 1), 4.32-4.23(m, 2), 4.09 (dd, J = 5.7, 10.2, 1), 3.87 (d, J = 3.0, 1), 3.54 (dd, J = 3.3, 10.2, 1), 2.24-2.15 (m, 1), 2.11 (s, 3), 0.99-0.96 (m, 6); MS (ESPOS): 483.5 $[M+H]^+$; MS (ESNEG): 481.4 $[M-H]^-$.

**[0250]** To a dry flask was added 13b (R1=Me, R2= Me, R3=H) (133.9 mg, 0.28 mmol, 1 equiv), triphenylphosphine (46.7 mg, 0.18 mmol, 0.64 equiv), copper (I) iodide (33.9 mg, 0.18 mmol, 0.64 equiv), palladium acetate (20 mg, 0.09 mmol, 0.32 equiv) and triethylamine (1.6 mL). The mixture was deaerated with nitrogen, followed by addition of 3-prop-2-ynyl-cyclopentane (120 mg, 1.11 mmol, 4 equiv). The mixture was stirred at 50 oC overnight. The solvent was removed under vacuum to give a dark residue. The residue was purified by chromatography to give 13c (R1=Me, R9'= 3-cyclopentyl-prop-1-ynyl, R2= Me, R3=H) as a yellow solid (106 mg, 83%): 1H NMR (300 MHz, $CD_3OD$) δ 8.55 (d, J = 4.8, 1), 7.98 (s, 1), 7.47 (dd, J = 1.7, 5.0, 1), 5.26 (d, J = 5.4, 1), 4.33-4.22 (m, 2), 4.10 (dd, J = 5.5, 10.4, 1), 3.86 (d,

J = 3.3, 1), 3.55 (dd, J = 3.3, 10.5, 1), 2.49 (d, J = 6.9, 2), 2.26-2.12 (m, 2), 2.11 (s, 3), 1.93-1.82 (m, 2), 1.73-1.55 (m, 4), 1.43-1.31 (m, 2), 1.00-0.96 (m, 6); MS (ESPOS): 463.6 $[M+H]^+$; MS (ESNEG): 461.5 $[M-H]^-$.

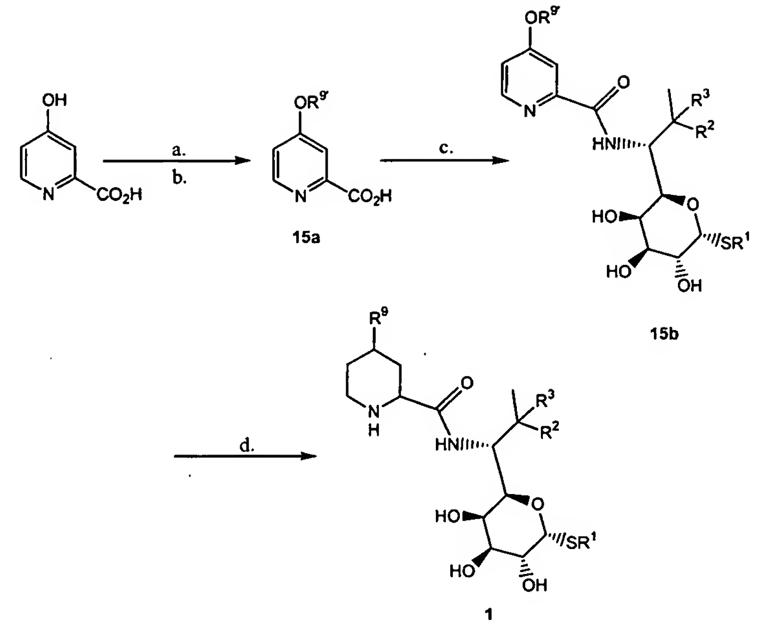


### Method R

**[0251]** To a solution of **13a** prepared in method Q (5 g, 13.26 mmol) in methanol (500 mL) was added a few drops of conc. sulfuric acid. The reaction mixture was refluxed overnight. The solvent was evaporated and the residue was purified by chromatography to give 4-iodopipecolinic acid methyl ester **14a** as a yellow solid (3.0 g, 86%): $^1$H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, J = 1.5, 1), 8.37 (d, J = 5.4, 1), 7.85 (dd, J = 1.6, 5.2, 1), 4.00 (s, 3); MS (ESPOS): 264.3 $[M+H]^+$.

**[0252]** To a dry flask were added **14a** (1 g, 3.8 mmol, 1 equiv), triphenylphosphine (79.7 mg, 0.3 mmol, 0.08 equiv), copper (I) iodide (57.9 mg, 0.3 mmol, 0.08 equiv), palladium acetate (34.1 mg, 0.15 mmol, 0.04 equiv) and triethylamine (14 mL). The mixture was deaerated with nitrogen, followed by addition of 3-butyn-1-ol (0.53 g, 7.6 mmol, 2 equiv). The mixture was stirred at rt for 3 h. The solvent was removed under vacuum to give a dark residue. The residue was purified by chromatography to give **14b** ($R^{9'}$= 3-hydoxy-but-1-ynyl) as a yellow oil (0.78 g, 100%): $^1$H NMR (300 MHz, $CDCl_3$) δ 8.66-8.63 (m, 1), 8.09-8.08 (m, 1), 7.43-7.40 (m, 1), 3.99 (s, 3), 3.88-3.82 (m, 2), 2.72 (t, J = 6.3, 2). MS (ESPOS): 206.4 $[M+H]^+$.

**[0253]** To a solution of the above **14b** ($R^{9'}$= 3-hydoxy-but-1-ynyl) (0.78 g, 3.8 mmol) in methanol (40 mL) was added 10 % palladium on carbon (0.4 g). The flask containing the reaction mixture was purged and charged with hydrogen (1 atm) and stirred at rt overnight. The palladium was removed by filtration and the filtrate was concentrated to give **14c** ($R^9$=3-hydroxybutyl) as an oil (0.77 g, 97%): $^1$H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, J = 4.5, 1), 7.97 (d, J = 1.2, 1), 7.29 (dd, J = 1.6, 5.0, 1), 3.99 (s, 3), 3.67 (t, J = 6.3, 2), 2.72 (t, J = 7.7, 2), 1.81-1.69 (m, 2), 1.62-1.54 (m, 2); MS (ESPOS): 210.4 $[M+H]^+$.



# Method S

[0254] To 4-hydroxypyridine-2-carboxylic acid **10b** ($R^9$ = hydroxy) (200 mg, 1.4 mmol) in DMF (2 mL), potassium carbonate (397 mg, 2.8 mmol) was added followed by *n*-bromobutane (197 mg, 1.4 mmol), warmed at 60°C for overnight. The solvent was removed to obtain the crude ester product. The crude ester (360 mg, 1.4 mmol) was dissolved in THF (4 mL), lithium hydroxide (72 mg, 1.7 mmol) was added, and the reaction mixture stirred at room temperature for 2 hr. The residue obtained on removal of solvent was purified by silica gel chromatography using 10% MeOH in DCM to provide 4-butoxypyridine-2-carboxylic acid **15a** ($R^{9'}$= butyl) (100 mg, 43%). $^1$H NMR (300 MHz, $CD_3OD$) δ 8.37 (d, *J*=6.0, 1), 7.63 (d, *J*=2.7, 1), 7.07 (dd, *J*=2.7, 6.0, 1), 4.15 (t, *J*=6.6, 2), 1.82 (m, 2), 1.54 (m, 2), 1.01 (t, *J*=7.5, 3). MS (ESNEG):194 $[M-H]^-$.

[0255] To 4-butoxypyridine-2-carboxylic acid **15a** ($R^{9'}$=Butyl) (100 mg, 0.5 mmol) in DMF (2 mL), 7-methyl α-thiolincosaminide **2b** ($R^1$=Me, $R^2$=Me) (147 mg, 0.5 mmol) was added, followed by HBTU (214 mg, 0.55 mmol) and DIEA (132 mg, 1 mmol). The reaction mixture was stirred at room temperature for 2 hr. The solvent was removed, and purification of the crude material was carried out by silica gel column chromatography to obtain compound **15b** ($R^1$=Me, $R^2$=Me, $R^{9'}$= butyl) (201 mg, 91%): $^1$H NMR (300 MHz, $CD_3OD$) δ 8.42 (m, 1), 7.96 (s, 1), 7.09 (m, 1), 5.27 (d, *J*=5.4, 1), 4.10-4.87 (m, 3), 3.85 (d, *J*=3.3, 1), 3.76 (m, 1), 2.11 (m, 4), 1.81 (m, 2), 1.49 (m, 4), 0.99 (m, 9). MS (METHOD ES+): 428 $[M+H]^+$.

[0256] To a solution of the pyridine **15b** ($R^1$=Me, $R^2$=Me, $R^{9'}$= butyl) (200 mg, 0.46 mmol) in water (10 mL), AcOH (3 mL) and MeOH (2 mL), was added $PtO_2$ (200 mg) and the resulting reaction mixture shaken under 55 psi hydrogen overnight. Residual catalyst was removed by filtration through celite, and the solvent was removed to obtain the crude product. Purification was carried out by silica gel column chromatography using 20% MeOH in DCM to obtain lincosamide analog **1** ($R^1$=Me, $R^2$=Me, $R^3$=H, $R^9$ = butoxy) (12 mg, 6%). $^1$H NMR (300 MHz, $CD_3OD$) δ 5.25 (d, *J*=5.4, 1), 4.22 (dd, *J*=10.2; 3.3, 1), 4.08 (m, 2), 3.81 (d, *J*=3.0, 1), 3.70 (m, 1), 3.54 (m, 4), 3.43 (m, 2), 2.90 (m, 1), 2.41 (m, 1), 2.19 (m, 1), 2.10 (s, 3) 1.45 (m, 6), 0.92 (m, 9); MS (ESPOS): 435 $[M+H]^+$.

## Method T

[0257] Following the general method found in scheme 16, to a solution of β-lactam **16a** (2.92 g, 12.8 mmol) 1 equiv; prepared from benzyl (*S*)-(–)-4-oxo-2-azetidine-carboxylate (Aldrich) as described by Baldwin et al, *Tetrahedron*, **1990**, *46*, 4733 in THF (30 mL) at 0 °C was added a solution of LDA (2.0 M, 14.0 mL, 28.1 mmol, 2.2 equiv) via syringe pump over 20 min. The reaction was stirred at 0 °C for 30 min., crotyl bromide (85%, 2.89 mL, 28.1 mmol, 2.2 equiv) was added dropwise over ca. 1.5 min, and the mixture was stirred for 2 h at 0 °C, and then partitioned between 1.0 M aqueous $KHSO_4$ (100 mL) and EtOAc (100 mL). The organic layer was separated and washed with 1.0 M aqueous $KHSO_4$ (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated to give **16b** ($R^{9'}$=2-butenyl) 3.65 g (100%) of greenish yellow solid. This material was used without further purification.

[0258] MS (ESNEG): 282.2 $[M - H]^-$.

[0259] (Trimethylsilyl)diazomethane (2.0 M in $Et_2O$, 25.0 mL, 50 mmol, 3.9 equiv) was slowly added to a solution of acid **16b** ($R^{9'}$=2-butenyl) (3.65 g, 12.9 mmol, 1 equiv) in methanol (70 mL) at 0 °C. Solvent was removed under vacuum to give 3.53 g (11.9 mmol, 92%) of the desired ester product as a yellow oil. This material was used in the subsequent reaction without further purification.

[0260] To a solution of alkene **16c** ($R^{9'}$=2-butenyl) (3.53 g, 11.9 mmol, 1 equiv) in EtOAc (40 mL) at 23 °C was added Pd/C (10 wt. %, 482 mg). The reaction vessel was charged with hydrogen (balloon), and the mixture stirred vigorously. After 2.5 h, the reaction mixture was filtered through a pad of Celite. Celite was washed, with EtOAc (200 mL) and the filtrate was concentrated to provide 3.51 g (11.7 mmol, 99%) of **16c** ($R^9$=butyl) as a yellow oil. This material was used without further purification.

[0261] MS (ESPOS): 300.4 $[M+H]^+$.

[0262] To a solution of *N*-TBS β-lactam **16c** ($R^9$=butyl) (3.51 g, 11.7 mmol, 1 equiv) in THF (50 mL) at 23 °C was added $Et_3N{\cdot}3HF$ (0.95 mL, 5.85 mmol, 0.5 equiv). After stirring for 60 min at 23 °C, the reaction mixture was partitioned between 90% saturated brine (150 mL) and EtOAc (200 mL). The organic layer was separated and washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated. The product was purified via flash column chromatography on silica gel using 50% EtOAc in hexane as eluent to give 1.48 g (8.0 mmol, 68%) of **16d** ($R^9$=butyl) as a clear oil.

[0263] MS (ESPOS): 578.3 $[3M+H]^+$.

[0264] To a solution of β-lactam **16d** ($R^9$=butyl) (2.06 g, 11.1 mmol, 1 equiv) in THF (150 mL) at 23 °C was added a solution of $LiAlH_4$ (1.0 M in THF, 22.9 mL, 22.9 mmol, 2.06 equiv) via syringe over the course of 2 min. After stirring for 10 min at 0 °C, the reaction was warmed to 23 °C, stirred for 15 min, and then refluxed for 3 h. The mixture was then cooled to 0 °C and quenched via careful addition of $H_2O$ (1.0 mL), followed by 15% aqueous NaOH (1.0 mL), and then $H_2O$ (2.5 mL). The resulting suspension was stirred at 23 °C for 1.5 h, diluted with $Et_2O$ (250 mL), and filtered through Celite, washing with $Et_2O$ (250 mL). The filtrate was concentrated to furnish 1.42 g of the desired product **16e** ($R^9$=butyl) (9.93 mmol, 89%) as a clear oil. The product was used without further purification.

[0265] MS (ESPOS): 287.4 $[2M+H]^+$.

[0266] To a solution of amino alcohol **16e** ($R^9$=butyl) (1.41 g, 9.86 mmol, 1 equiv) in dichloromethane (50 mL) at 23 °C was added $Boc_2O$ (2.59 g, 11.9 mmol, 1.2 equiv). After stirring for 2 h at 23 °C, the reaction mixture was concentrated. The product was purified via flash column chromatography on silica gel using 33% EtOAc in hexane as eluent to give 1.53 g (6.31 mmol, 64%) **16f** ($R^9$=butyl) as a clear oil.

[0267] MS (ESPOS): 266.0 $[M + Na]^+$.

[0268] To a solution of $NaIO_4$ (8.81 g, 41.2 mmol, 10 equiv) in $H_2O$ (60 mL) at 23 °C was added $RuCl_3{\cdot}xH_2O$ (350 mg, catalytic amount) followed by a solution of alcohol **16f** ($R^9$=butyl) (1.00 g, 4.12 mmol, 1 equiv) in acetone (60 mL). The biphasic mixture was stirred for 30 min at 23 °C, then extracted with EtOAc (250 mL), decanting the organic layer. The aqueous residue was extracted with two further portions of EtOAc (2 × 150 mL). The combined organic extracts were treated with 2-propanol (75 mL) and stirred at 23 °C. After stirring for 2 h the mixture was filtered through Celite, washing with EtOAc (300 mL). The filtrate was concentrated to furnish

0.78 g of the desired product **16g'** ($R^9$=butyl) (3.04 mmol, 74%) as a dark oil. The product was used without further purification. MS (ESPOS): 280.0 $[M + Na]^+$.

### Method U

[0269] Following the method shown in general scheme 17, to a solution of alcohol **16f** ($R^{9'}$=2-methyl-2-butenyl) (3.31 g, 13.0 mmol, 1 equiv) in DMF (100 mL) at 23 °C was added imidazole (2.21 g, 32.5 mmol, 2.5 equiv) followed by TBSCl (2.93 g, 19.5 mmol, 1.5 equiv). The reaction was stirred for 35 min and then quenched with MeOH (2.0 mL). After stirring for 5 min, the resulting mixture was partitioned between $Et_2O$ (500 mL) and $H_2O$ (400 mL). The organic layer was separated and washed with $H_2O$ (400 mL), brine (200 mL), dried ($MgSO_4$), filtered and concentrated to give **17a** ($R^{9''}$=2-methyl-2-butenyl) 4.13 g (11.2 mmol, 86%) of the desired product as a clear oil.

[0270] MS (ESPOS): 392.4 $[M + Na]^+$.

[0271] A solution of intermediate **17a** ($R^{9'}$=2-methyl-2-butenyl) prepared as described in general method T (2.03 g, 5.50 mmol, 1 equiv) in dichloromethane (80 mL) at –78 °C was treated with ozone (1.2 L/min) introduced via a gas dispersion tube until a blue color was observed (20 min). A stream of oxygen (1.2 L/min) was then passed through the reaction mixture to discharge excess ozone. After 15 min, oxygen flow was ceased and $PPh_3$ (2.16 g, 8.25 mmol, 1.5 equiv) was added. The reaction mixture was stirred at –78 °C for 30 min, then at 0 °C for 15 min, and then warmed to 23 °C. After stirring for 10 min at 23 °C, silica gel was added, and the resulting mixture concentrated to dryness under vacuum to afford a free-flowing powder that was loaded directly onto a silica gel column. Flash column chromatography using 30–33% EtOAc in hexane as eluent gave 1.52 g (4.42 mmol, 80%) of **17b** as a clear oil.

[0272] MS (ESPOS): 398.0 $[M + MeOH + Na]^+$.

[0273] To a suspension of Wittig salt (cyclopropylmethyl triphenyl phosphine) (1.216 g, 3.06 mmol, 1.5 equiv) in THF (10 mL) at 0 °C was added a solution of NaHMDS (1.0 M in THF, 3.06 mL, 3.06 mmol, 1.5 equiv) dropwise via syringe over the course of 1 min. The resulting solution was stirred for 20 min at 0 °C then treated with a solution of aldehyde **17b** (700 mg, 2.04 mmol, 1 equiv) in THF (3.0 mL; 2 × 1.0 mL flush) transferred via canula. After 15 min at 0 °C the reaction was warmed to 23 °C, stirred for a further 10 min then quenched with saturated $NH_4Cl$ (30 mL). The resulting mixture was partitioned between $Et_2O$ (120 mL) and $H_2O$ (50 mL). The organic layer was separated and washed with brine (50 mL), dried ($MgSO_4$)

filtered and concentrated. Flash column chromatography using 10% EtOAc in hexane as eluent gave 588 mg (1.54 mmol, 76%) of **17c** ($R^{9'}$=2-(3-cyclopropyl)-propen-1-yl) as a clear oil.

**[0274]** MS (ESPOS): 404.3 $[M + Na]^+$.

**[0275]** To a solution of TBS ether **17c** ($R^{9'}$=2-(3-cyclopropyl)-propen-1-yl) (190 mg, 0.50 mmol, 1 equiv) in THF (10 mL) at 23 °C was added a solution of TBAF (1.0 M in THF, 0.55 mL, 0.55 mmol, 1.1 equiv). The resulting solution was stirred for 40 min at 23 °C then partitioned between $Et_2O$ (50 mL) and $H_2O$ (50 mL). The organic layer was separated and washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated to give 133 mg (0.50 mmol, 100%) of **17c** ($R^{9'}$=2-(3-cyclopropyl)-propen-1-yl) as a clear oil.

**[0276]** MS (ESPOS): 290.2 $[M + Na]^+$.

**[0277]** To a solution of alkene **17c** ($R^{9'}$=2-(3-cyclopropyl)-propen-1-yl) (191 mg, 0.50 mmol, 1 equiv) in dioxane (5.0 mL) at 23 °C was added dipotassium azodicarboxylate (973 mg, 5.01 mmol, 10 equiv) followed by slow addition of a solution of AcOH (573 μL, 10.0 mmol, 20 equiv) in dioxane (5.0 mL) over the course of 16 h via syringe pump. Following the completion of the addition the reaction was stirred a further 6 h then filtered through a glass frit with the aid of $Et_2O$ (150 mL) to remove precipitate. The resulting solution was washed with saturated aqueous $NaHCO_3$ (2 × 100 mL), brine (80 mL), dried ($MgSO_4$), filtered and concentrated. The above procedure was repeated three times on the crude material obtained to give complete conversion of the alkene, providing 183 mg (0.48 mmol, 96%) of the saturated product **17d** ($R^9$=3-cyclopropyl-propyl) as a clear oil.

**[0278]** MS (ESPOS): 406.0 $[M + Na]^+$.

**Method V**

**[0279]** Following the general method in Scheme 18, to a solution of the compound **1** hydrochloride (wherein $R^1$=$R^2$ =Me, $R^3$=H, $R^6$=H, $R^9$=4-*cis*-n-Pr, and m=2) (4.00 g, 9.90 mmol, 1 equiv) in THF (70 mL) at 23 °C was added $H_2O$ (70 mL) followed by $KHCO_3$ (1.29 g, 12.9 mmol, 1.3 equiv) followed by $(Boc)_2O$ (2.81 g, 12.9 mmol, 1.3 equiv). After stirring for 5 h, the reaction mixture was partitioned between brine (200 mL) and EtOAc (300 mL). The organic layer was separated and washed with brine (150 mL), and dried ($MgSO_4$). Solvent was removed under vacuum and the crude product purified using Biotage® column chromatography system (40+M cartridge, 40 mm ID x 150 mm) using a linear gradient (75% EtOAc/hexanes–100% EtOAc) over 1.2 L total eluent at 50 mL/min to give 4.49 g of the pure carbamate **18a** (wherein $R^1$=$R^2$ =Me, $R^3$=H, $R^9$=4-*cis*-n-Pr, and m=2) (8.91 mmol, 90%).

[0280] To a solution of carbamate **18a** (wherein $R^1$=$R^2$ =Me, $R^3$=H, $R^9$=4-*cis*-n-Pr, and m=2) (7.99 g, 15.9 mmol, 1 equiv) in benzene (300 mL) at 23 °C was added *p*-anisaldehyde dimethyl acetal (4.06 mL, 23.8 mmol, 1.5 equiv), followed by PPTS (199 mg, 0.79 mmol, 0.05 equiv). The reaction mixture was heated to reflux. After 4 h a second portion of *p*-anisaldehyde dimethyl acetal (2.0 mL, 11.7 mmol, 0.74 equiv) was added. After a further 17 h a third portion of *p*-anisaldehyde dimethyl acetal (2.0 mL, 11.7 mmol, 0.74 equiv) was added. Following the final addition the reaction was refluxed a further 3 h then cooled to 23 °C and partitioned between EtOAc (300 mL) and $H_2O$ (300 mL). The organic layer was washed with 50% saturated aqueous $NaHCO_3$ (300 mL), brine (150 mL), dried ($MgSO_4$), filtered and concentrated. The crude product was purified via silica gel flash column chromatography using 40% EtOAc in hexane as eluent to give acetal **18b** (wherein $R^1$=$R^2$ =Me, $R^3$=H, $R^9$=4-*cis*-n-Pr, and m=2) 7.00 g (11.3 mmol, 71%) of the desired product as a white foam (1:1 ratio of diastereomers). A small portion of the product was purified on Biotage® column chromatography system (40+S cartridge, 40 mm ID x 75 mm) using a linear gradient (5% EtOAc/hexanes–90% EtOAc/hexanes) over 1.2 L total eluent at 50 mL/min to separate the two diastereomers for characterization.

[0281] Diastereomer with high $R_f$: MS (ESPOS): 623.0 $[M+H]^+$.

[0282] Diastereomer with low $R_f$: MS (ESPOS): 623.0 $[M+H]^+$.

[0283] To a solution of alcohol **18b** (wherein $R^1$=$R^2$ =Me, $R^3$=H, $R^9$=4-*cis*-n-Pr, and m=2) (3.00 g, 4.82 mmol, 1 equiv) in trimethyl phosphate (60 mL) at 0 °C was added pyridine (3.90 mL, 48.2 mmol, 10 equiv), followed by $POCl_3$ (0.88 mL, 9.65 mmol, 2 equiv) added over the course of 60 sec. Following the addition, the reaction was maintained at 0 °C for 2 h, then triethylammonium bicarbonate buffer (1.0 M, pH 8.5, 40 mL) was added carefully to quench the reaction. $H_2O$ (60 mL) was then added, and the resulting mixture was stirred at 0 °C for 30 min then warmed to 23 °C. After stirring the quenched reaction mixture for 2 h at 23 °C, volatiles were removed in vacuo with aid of gentle heating in water bath (40–45 °C). The resulting crude product was azeotropically dried by co-evaporation with DMF (3 × 100 mL), then toluene (150 mL, bath temperature=40–45 °C) to provide 9.4 g of white solid. The crude product **18c** (wherein $R^1$=$R^2$ =Me, $R^3$=H, $R^9$=4-*cis*-n-propyl, $R^{11}$=$PO(OH)_2$ and m=2) was substantially contaminated with triethylammonium salts, but was carried forward without purification.

[0284] MS (ESNEG): 701.2 $[M-H]^-$.

[0285] To a solution of the protected phosphate **18c** (wherein $R^1$=$R^2$ =Me, $R^3$=H, $R^9$=4-*cis*-n-propyl, $R^{11}$=$PO(OH)_2$ and m=2) prepared as described above (9.4 g, crude from previous step,

approximately 4.8 mmol) in 1,2-dichloroethane (600 mL) at 0 °C was added $H_2O$ (25 mL) followed by TFA (200 mL). Following the additions, the reaction was maintained at 0 °C for 5 min then warmed to 23 °C. After stirring for 25 min at 23 °C, volatiles were removed in vacuo to give 16.2 g of oil. The crude product was dissolved in 1:1 $H_2O$/MeOH (70 mL), filtered and the resulting solution was purified by preparative HPLC (Waters Nova-Pak® HR $C_{18}$, 6 µm particle size, 60 Å pore size, 40 mm ID × 200 mm, 5–60% acetonitrile in $H_2O$ w/ 0.1% AcOH over 30 min, 75 mL/min flow rate) to give 1.497 g of the desired phosphate **5** (wherein $R^1$=$R^2$ =Me, $R^3$=H, $R^9$=4-*cis*-n-propyl, $R^{11}$=$PO(OH)_2$) (3.10 mmol, 64% from free alcohol) as a white solid.

**Method W**

**[0286]** Following the general method outlined in Scheme 19, to amino acid **19a** ($R^{12}$=H) (Aldrich) (1.0 g, 8.7 mmol) suspended in MeOH (5 mL) and 2,2-dimethoxypropane (15 mL) was added concentrated HCl (1.0 mL), and the mixture was stirred 12 h at r.t.. Solvents were removed under vacuum, and the residue was triturated with $Et_2O$ and co-evaporated from dry toluene to furnish the crude methyl ester as an off-white solid which was used without further purification.

**[0287]** To a suspension of crude L-allylglycine methylester in dichloroethane (32 mL) at 0 °C was added 2,4,6-collidine (2.3 mL, 19.1 mmol, 2.2 equiv) and solid 2-nitrobenzenesulfonyl chloride. The reaction was stirred for 3 h at r.t. The solvent was removed under vacuum and the residue was distributed between EtOAc (200mL) and sat. aqueous $NH_4Cl$. The organic layer was washed with 1.0 M aq. $KHSO_4$, sat. aq. $NaHCO_3$, brine, and dried ($MgSO_4$), and concentrated to give a residue that was purified by column chromatography on silica (gradient 10 to 20% EtOAc/hexanes) to give the desired product **19b** ($R^{12}$=H) 0.70 g (26 %) as a yellow oil.

**[0288]** $^1$H NMR (300 MHz, $CDCl_3$) δ 8.10-8.06 (m, 1), 7.95-7.92 (m, 1), 7.76-7.73 (m, 2), 6.08 (d, *J*=8.2, 1), 5.74-5.60 (m, 1), 5.17-5.12 (m, 2), 4.33–4.26 (m, 1), 3.52 (s, 3), 2.58 (dd, *J*=6.0, 6.0, 1), 3.44–3.30 (m, 2), 2.25–2.10 (m, 2), 2.11 (s, 3), 2.00–1.88 (m, 1), 1.86–1.70 (m, 1), 1.44–1.25 (m, 6), 0.98–0.88 (m, 9 H). MS (ESNEG): 313.0 $[M-H]^-$.

**[0289]** To a stirred suspension of sulfonamide **19b** ($R^{12}$=H) (685 mg, 2.18 mmol), $Cs_2CO_3$ (710 mg, 2.18 mmol), and tetrabutylammonium bromide (702 mg, 2.18 mmol), in DMF (5.0 mL) was added a solution of 3-methylenehex-1-yl-toluenesulfonate (702 mg, 2.61 mmol; prepared as described by Kelvin H. Yong et al. *Journal of Organic Chemistry*, **2001**, *66*, 8248)

in DMF (1.0 mL), the reaction mixture was heated to 60 °C overnight. The reaction solvent was removed by evaporation, the resulting residue taken up in EtOAc and washed with 10% aqueous citric acid and brine, the organic phase was dried over $MgSO_4$ concentrated to give a residue that was purified by column chromatography on silica (17%–20% EtOAc/hexanes) to give the desired product **19c** ($R^{12}$=H, $R^{13}$=propyl), (0.38g, 42 %) as an oil.

**[0290]** MS (ESPOS): 433 $[M + Na]^+$.

**[0291]** To a solution of **19c** ($R^{12}$=H, $R^{13}$=propyl) (0.38 g, 0.92 mmol) in anhydrous DCM (40 mL) was added benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene] dichloro-(tricyclohexylphosphine)ruthenium (23.3 mg, 0.0276 mmol). The resulting reaction mixture was refluxed under $N_2$ for 2.5 hrs, cooled to room temperature and concentrated. The product was purified by flash column chromatography on silica gel (35% ethyl acetate/hexanes) to give the desired compound **19d** ($R^{12}$=H, $R^{13}$=propyl) (0.29 g, 81 %).

**[0292]** MS (ESPOS): 383 $[M + Na]^+$.

**[0293]** To a stirred solution of thiophenol (183 μL, 1.79 mmol) and 7-methyl-1,5,7-triazabicyclo-[4,4,0] dec-5-ene (214 μL, 1.49 mmol) in anhydrous DMF (3 mL) was added a solution of alkene **19d** ($R^{12}$=H, $R^{13}$=propyl) (228 mg, 0.596 mmol) in anhydrous DMF (3.0 mL) via a canula. A color change to yellow was observed upon the mixing of the solutions, the resulting reaction mixture was stirred under $N_2$ for one hour then concentrated to a residue. The residue was taken up in ether, stirred with 1N aqueous HCl (15.0 mL) for 5 min. The aqueous phase was washed with ether then made basic with solid potassium carbonate. The resulting basic aqueous phase was extracted with ether three times. The combined organic layer was washed with brine, dried with anhydrous sodium sulfate, concentrated, cooled to 0 °C, treated with 2M HCl in ether (0.8 mL), and the resulting mixture was stirred for 5 min and then evaporated to dryness to give the desired product **19d** ($R^{12}$=H, $R^{13}$=propyl) as the hydrochloride salt (144 mg, 103%).

**[0294]** MS (ESPOS): 198 $[M+H]^+$.

**[0295]** To a solution of amine **19d** ($R^{12}$=H, $R^{13}$=propyl) (143 mg, 0.61 mmol) in anhydrous dichrolomethane (2.0 mL) was added triethylamine (170 μL, 1.22 mmol) and di-*t*-butyldicarbonate (350 mg, 1.6 mmol). The resulting reaction mixture was stirred over night at room temperature under $N_2$ then evaporated to dryness and purified by flash column chromatography on silica gel using 20% ethylacetate in hexanes as an eluent to give the desired compound **19e** ($R^{12}$=H, $R^{13}$=propyl) (176 mg, 86%).

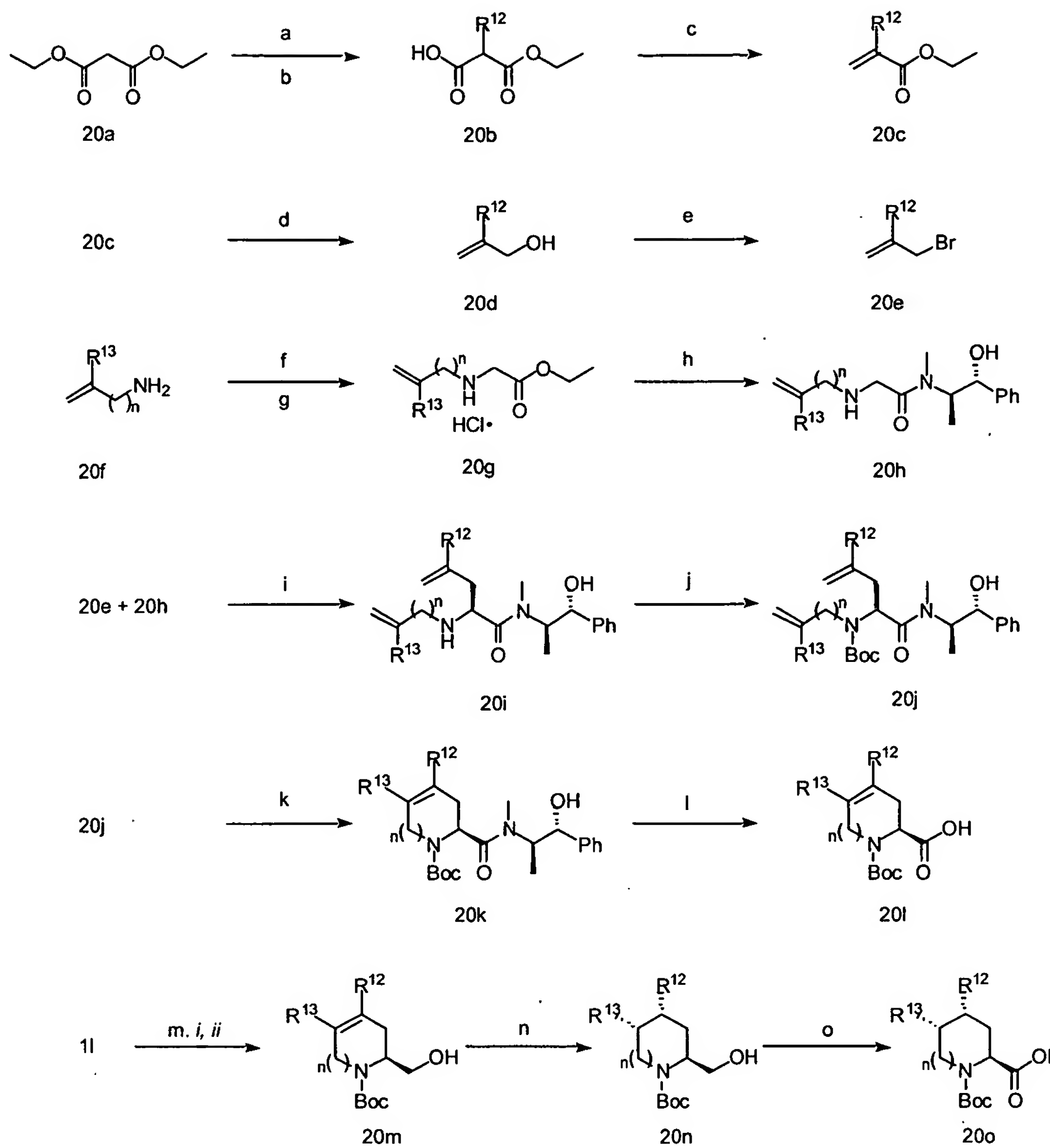
**[0296]** MS (ESPOS): 320 $[M + Na]^+$.

[0297] To a solution of ester **19e** ($R^{12}$=H, $R^{13}$=propyl) (175 mg, 0.59 mmol) in dioxane/water (6:1) (4 mL) was added 1 M aqueous lithium hydroxide (0.65 mL, 0.648 mmol). The resulting reaction mixture was stirred over night at room temperature under $N_2$ and the solvent was removed under reduced pressure. The residue was taken up in water washed with ether. The aqueous layer was acidified with 10% citric acid and extracted with ether. The organic layer was washed with brine, dried with sodium sulfate, and evaporated to dryness to give the desired protected cyclic amino acid **19f** ($R^{12}$=H, $R^{13}$=propyl) (175 mg, 105 %).

[0298] MS (ESNEG): 292 $[M-H]^-$.

**Method X**

[0299] As shown in Scheme 20 below, suitable amino esters **20g** n=1,2 may be appended with psuedoephedrine which serves as a chiral auxiliary, allowing stereospecific alkylation of the α carbon with a suitable allylic bromide **20e**. Protection of the secondary amine followed by olefin metathesis and cleavage of the chiral auxiliary leads to 4,5 unsaturated N-protected cyclic amino acids **20l**. Reduction of the 2-carboxylic acid to a hydroxymethyl allows stereospecific *trans*-reduction of the 4,5 unsaturation in which leads to **20n.** Re-oxidation of the hydroxymethyl to a carboxylic acid in which $R^{12}$ or $R^{13}$ may be $R^9$ as defined in formula I.



**Scheme 20.** General stereospecific synthesis of *trans*-alkylpiperidine-2-carboxylic acids (n=1) and *trans*-alkylazapine-2-carboxylic acids (n=2).

**[0300]** The following general reaction scheme may be used in the preparation of *trans*-alkylpiperidine-2-carboxylic acids and *trans*-alkylazapine-2-carboxylic acids: (a) NaH, DMF; R–Br, 65 °C; (b) 1 M aqueous KOH, EtOH, 80 °C; (c) $CH_2O$, piperidine, EtOH, 80 °C; (d) DIBALH, $CH_2Cl_2$, -50 °C; (e) $PBr_3$, pyridine, $Et_2O$, 0 °C; (f) Ethyl bromoacetate, $Et_2O$, 23 °C; (g) 4.0 M HCl in dioxane, $Et_2O$, hexane, 23 °C; (h), (1*R*,2*R*)-(–)-Pseudoephedrine, *t*-BuOLi, THF, 23 °C; (i) LiHMDS, LiCl, THF, 0 °C; (j) $(Boc)_2O$, $Et_3N$, $CH_2Cl_2$, 23 °C; (k) Benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro-(tricyclohexylphosphine)ruthenium, $CH_2Cl_2$, 23 °C; (l) 1 M Aq. NaOH, MeOH, 70 °C; (m) (i)

Isobutyl chloroformate, 4-methylmorpholine, DME, -15 °C, (ii) $NaBH_4$, $H_2O$, 0 °C; (n) $H_2$, $IrCODPyPCy_3.PF_6$, $CH_2Cl_2$, 23 °C; (o) $RuCl_3.xH_2O$, $NaIO_4$, acetone, $H_2O$, 23 °C.

**[0301]** As shown in Scheme 20, suitable amino esters **20g** n=1,2 may be appended with psudoephedrine which serves as a chiral auxiliary, allowing stereospecific alkylation of the $\alpha$ carbon with a suitable allylic bromide **20e**. Protection of the secondary amine followed by olefin metathesis and cleavage of the chiral auxiliary leads to 4,5 unsaturated N-protected cyclic amino acids **20l**. Reduction of the 2-carboxylic acid to a hydroxymethyl allows stereospecific *trans*-reduction of the 4,5 unsaturation in which leads to **20n**. Re-oxidation of the hydroxymethyl to a carboxylic acid in which $R^{12}$ or $R^{13}$ may be $R^9$ as defined in general structure.

## Method Y

**[0302]** Following the general reaction scheme 21, a rapidly stirred solution of 4-oxo-piperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester **21a** (m=2, P=H, $P_2$=Boc) (16.0 g, 0.066 mol) (prepared by the method described by Bousquet et al. *Tetrahedron*, **1997**, *53*, 15671) in DMF (200 mL) was treated with solid cesium carbonate (10.7 g, 0.033 mol) and methyl iodide (4.5 mL, 0.072 mol). The reaction mixture was stirred 5h, diluted with EtOAc and extracted with sat. aq. sodium bicarbonate, 10% aq. citric acid and brine, the organic layer was separated and dried over sodium sulfate, friltered and evaporated to dryness. The product obtained on removal of solvent was azeotropically dried by evaporation from dry benzene to afford 14.8 g (98%) of the desired product 4-Oxo-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester **21a** (m=2, P=Me, $P_2$= Boc) as an oil: TLC $R_f$ 0.53 (Hexanes/EtOAc, 1:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.33 (broad m, 0.5) rotamer, 5.06 (broad m, 0.5) rotamer, 4.31-4.19 (m, 1), 3.95 (s, 3), 3.95-3.70 (m, 1), 3.16-2.97 (m, 2), 2.71 (m, 2), 1.68 (broad s, 9).

**[0303]** A 0 °C stirred solution of 4-oxo-piperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester **21a** (m=2, P=Me, $P_2$=Boc) (5.17 g, 0.02 mol) in DCM (60 mL) was treated with tetraallyltin (Aldrich) (5.3 mL, 0.022 mol) followed by dropwise addition of $BF_3 \bullet OEt_2$ (2.5 mL, 0.02 mol). The reaction mixture was stirred 1h, then aq. 1M potassium fluoride (38.0 mL) and celite (5 g) was added and the reaction mixture was stirred 3h. The reaction mixture was filtered and concentrated to dryness, the residue was dissolved in DCM and washed with water and brine, dried over $MgSO_4$ and evaporated to dryness. The residue obtained was purified by silica gel column chromatography (DCM 100% to DCM: acetone 9:1) to afford 3.85 g (64%) of the desired product 4-allyl-4-hydroxy-piperidine-1,2-dicarboxylicacid 1-tert-butyl ester 2-methyl ester **21b** (m=2, P=Me, $P_2$=Boc, $R^{9'}$=allyl) as an oil.

[0304] $^1$H NMR (300 MHz, $CDCl_3$) δ 6.11-5.97 (m, 1), 5.42-5.32 (m, 2), 5.06 (broad d, J = 6.0, 0.5) rotamer, 4.87 (broad d, J = 6.0, 0.5) rotamer, 4.18-4.03 (m, 1), 3.93 (s, 3), 2.48-2.37 (m, 2), 1.98-1.43 (m, 11); MS (ESPOS): 322.0 $[M+Na]^+$.

[0305] A stirred suspension of **21b** (m=2, P=Me, $P_2$= Boc, $R^{9'}$=allyl) (3.80 mL, 1.27 mmol) and 10% Pd/C (degusa wet form 50% w/w) (1.35 g, 1.3 mmol) in MeOH (80 mL) was stirred 6h under 1 atm hydrogen. The reaction mixture was filtered through celite and evaporated to dryness and dried azeotropically by evaporation from toluene the residue obtained (3.15 g) was used in the next step without further purification.

[0306] To a stirred -78°C solution of DAST (1.7 mL, 1.3 mmol) in DCM (50 mL) was added 4-Hydroxy-4-propyl-piperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester in DCM (30 mL). The reaction mixture was then stirred for 1h, then allowed to warm to -40°C for 5h. Additional DAST (0.4 mL) was added and the reaction mixture was stirred an additional 2h, sat. aq. $K_2CO_3$ (20 mL), and water (60 mL) were added followed by diethyl ether (500mL). The organic layer was separated, washed with brine, dried over sodium sulfate and evaporated to dryness. The resulting crude fluorinated product was purified by silica gel column chromatography (hexanes-EtOAc 9:1). The residue obtained by chromatographic purification was dissolved in dioxane (65 mL) and water (26 mL), cooled to 0°C, and treated with $OsO_4$ (0.65 mL, 4% aq. solution) and 30% $H_2O_2$ (10 mL). The reaction mixture was stirred overnight and concentrated to dryness. The residue was dissolved in DCM and the organic layer washed with water (100 mL), 25% aq. $Na_2SO_3$ (2x100 mL), and brine (100 mL), dried over $Na_2SO_4$ and evaporated to dryness. The residue obtained was purified by silica gel column chromatography (hexanes-EtOAc 9:1) to afford (1.08 g, 34 %) of the desired product 4-fluoro-4-propyl-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester **21c** (m=2, P=Me, $P_2$= Boc, $R^9$= *n*-propyl) as an oil.

[0307] $^1$H NMR (300 MHz, $CDCl_3$) δ 4.59 (dd, *J*=6.0, 6.0, 1), 3.82-3.69 (m, 1), 3.74 (s, 3), 3.28 (m, 1), 3.29-2.04 (m, 2), 1.91-1.71 (m, 3), 1.60-1.31 (m, 6), 1.45 (s, 9), 0.92 (t, *J*=7.1, 3); MS (ESPOS): 204.1 (M+H-Boc), 326.3 $[M+Na]^+$.

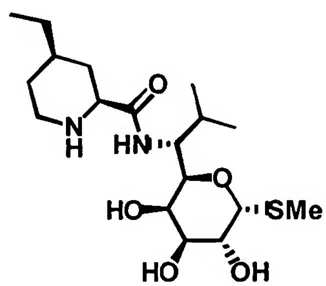
[0308] A stirred solution of **21c** (m=2, $P_2$= Boc, $R^9$=*n*-propyl) (1.06 g, 3.47 mmol) in dioxane-water 6:1 (42 mL) was treated with 1.0 M aq. lithium hydroxide (5.3 mL, 5.3 mmol). The reaction mixture was stirred at room temperature overnight, then treated with additional 1.0 M aq. lithium hydroxide (1.5 mL) and the resulting reaction mixture was stirred 5h. The reaction solvent was removed, the residue was taken up in ethyl acetate (500 mL), washed with 10% Citric acid and brine and dried over $MgSO_4$. Concentration of organic solution to afford

the desired product 4-fluoro-4-propyl-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester **21d** (m=2, $P_2$=Boc, $R^9$=*n*-propyl) (0.88 g, 87 %) as a white solid.

**[0309]** $^1$H NMR (300 MHz, $CDCl_3$) δ 4.59 (dd, *J*=6.0, 6.0, 1), 3.82-3.69 (m, 1), 3.74 (s, 3), 3.28 (m, 1), 3.29-2.04 (m, 2), 1.91-1.71 (m, 3), 1.60-1.31 (m, 6), 1.45 (s, 9), 0.92 (t, *J*=7.1, 3); MS (ESNEG): 288.4 $[M-H]^-$.

## Example 1

### Preparation of 1-(4-ethylpiperid-6-yl)-N-{1- [3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide




**[0310]** 4-Ethyl pyridine-2-carboxylic acid HCl salt (Toronto) (117 mg, 0.64 mmol) was suspended in dry acetonitrile (4 mL). Triethylamine (180 µL, 1.28 mmol) was added and the reaction mixture was cooled to 0°C. Isobutyl chloroformate (129 µL, 0.62 mmol) was added and the reaction mixture was warmed to 4°C. After 1.5 h the activated ester solution was transferred to a solution of **2b** ($R^1$=Me, $R^2$=Me), prepared as in Method C, in 1:1 acetone/water (2 mL) and warmed to 30°C to dissolve. Triethylamine (80 µL, 0.057 mmol) was then added to the reaction mixture. The reaction mixture was stirred for 10 h at rt, then evaporated to dryness and chromatographed on silica 94:5 dichloromethane:0.25% ammonia in methanol to provide **11b** ($R^1$=Me, $R^2$=Me $R^3$=H, $R^9$=ethyl) (167 mg 69.7%).

MS (ESPOS): 385.2 $[M+H]^+$.

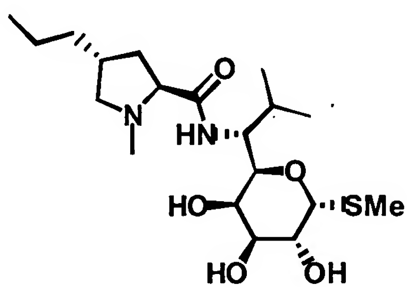
**[0311]** A solution of pyridine **11b** (m=2, $R^1$=Me, $R^2$=Me $R^3$=H, $R^9$=ethyl) (167 mg, 0.435 mmol) in 3:2 methanol/water (20 mL) was added to platinum(IV)oxide (339 mg, 0.521 mmol) in a Parr bottle. Concentrated HCl (52 µL, 0.52 mmol) was then added. The bottle was purged, and charged with $H_2$ to 65 psi and shaken for 24 h. The reaction mixture was filtered through celite and rinsed with methanol. The combined filtrate was evaporated to dryness and chromatographed on silica 88:12 to 80:20 dichloromethane: 0.25% ammonia in methanol to give 43 mg of a high $R_f$ product and 49 mg of a mixed fraction. Chromatography of the low $R_f$

fraction on fluorosil 84:16 to 80:20 dichloromethane: 0.25% ammonia in methanol provided 1-(6-(S)-4-(R)-ethylpiperid-6-yl)-N-{1-(R)- [2-(S)-3-(S),4-(S),5-(R)-trihydroxy-6-(R)-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide (21.9 mg, 12.9%), which was taken up in 1:1 acetonitrile:water (50 mL), 0.2μ millipore filtered, and cooled to 0°C. 1N HCl (67 μL) in water (20 mL) was added and re-lyophilized to provide the HCl salt (24.0 mg) as a colorless powder.

**[0312]** $^{1}$H NMR (300 MHz, $D_2O$) δ 5.32 (d, J = 5.8, 1), 4.14-4.06 (m, 1), 4.12 (s, 2), 3.85 (d, J = 3.30, 1), 3.60 (dd, J = 3.3, 10.4, 1), 3.30 (dd, J = 2.5, 11.8, 1), 3.09 (m, 1), 2.56 (ddd, J = 2.8, 12.9, 15.7, 1), 2.14 (s, 3), 2.14-2.05 (m, 1), 1.96-1.90 (m, 1), 1.74-1.69 (m, 1), 1.45-1.35 (m, 1), 1.33-1.23 (m, 2), 1.08-0.98 (m, 2), 0.86 (m, 9); MS(ESPOS): 391.4 $[M+H]^+$, 803.5.4 [2M+Na], (ESNEG): 389.5 $[M-H]^-$.

## Example 2

## Preparation of 1-(-4-n-propyl-N-methylpyrrolidin-2-yl)-N-{1- [3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide



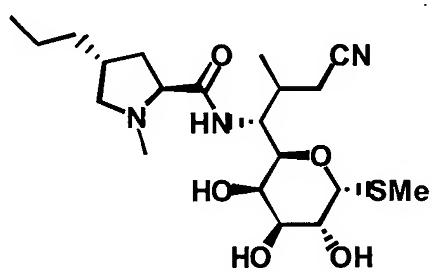
**[0313]** 4-n-Propylhygric acid prepared by the method of Hoeksema, H. et. al. Journal of the American Chemical Society, **1967**, 89 2448-2452 (157 mg, 0.76 mmol) was suspended in dry acetonitrile (5 mL). Triethylamine (421 μL, 3.02 mmol) was added and the reaction mixture was cooled to 0°C. Isobutyl chloroformate (98 μL, 0.76 mmol) was added and after 10 min the reaction was allowed to warm to 4°C. After 1.5 h a solution of **2b** ($R^1$=Me, $R^2$=Me), from Method C (190 mg, 0.76 mmol) in 1:1 acetone:water (5 mL) was added and the reaction mixture was stirred for 10h at rt. The reaction mixture was evaporated to dryness and chromatographed on silica 94:6 dichloromethane:0.25% ammonia in methanol. Fractions 14-18 contained the product as a colorless oil (50.2 mg, 16.5%).

**[0314]** $^{1}$H NMR (300 MHz, $D_2O$) δ 5.33 (d, J = 6.0, 1), 4.27-4.22 (m, 1), 4.18 (s, 1), 4.09 (dd, J = 5.8, 10.2, 1), 3.92-3.81 (m, 1), 3.92-3.81 (m, 1), 3.64-3.59 (m, 1), 2.92 (s, 3), 2.92-2.85

(m, 1), 2.35-2.28 (m, 3), 2.13 (s, 3), 1.46-1.41 (m, 2), 1.40-1.28 (m, 2), 0.89-0.84 (m, 9); MS(ESPOS): 405.5 $[M+H]^+$.

## Example 3

### Preparation of 1-(-4-n-propyl-N-methylpyrrolidin-2-yl)-N-{1- [3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methyl-3-cyanoprop-1-yl}acetamide

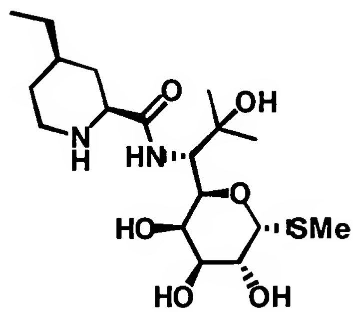


[0315] Lincosamine **2b** ($R^1$=Me, $R^2$=$CH_2CN$) (54.2 mg, 0.20 mmol) prepared by Method E was dissolved in DMF (0.7 mL). The reaction mixture was cooled to 0°C and triethylamine (170 µL, 1.2 mmol) and BSTFA (96 µL, 0.36 mmol) was added. The reaction mixture was allowed to warm to rt, and stirred at rt for 1 h. 4-n-Propylhygric acid prepared by the method of Hoeksema, et al., J. Am. Chem. Soc., **1967**, 89 2448-2452 (66.4 mg, 0.32 mmol) and HATU (149 mg, 0.39 mmol) were added, and the mixture was stirred at rt for 3 h. DMF was removed and the residue was dissolved in DCM (100 mL), washed with saturated $NaHCO_3$ (30 mL) and brine (30 mL), and dried over sodium sulfate. The residue obtained by removing the solvent was dissolved in methanol (20 mL) and treated with Dowex resin $H^+$ (300 mg) for 15 min. The crude product was eluted from the resin by washing with 5% TEA in MeOH (25 mL x 15 min x 2) and 5% TEA in MeCN (25 mL x 15 min). The combined eluent was evaporated to dryness and purified by silica gel column chromatography using 7% 0.25M $NH_3$ in methanol in dichloromethane as the eluent (24 mg, 28%).

[0316] $^1$H NMR (300 MHz, $D_2O$) δ 5.61 (d, J = 5.8, 1), 4.59 (d, J = 10.2, 1), 4.46 (d, J = 10.2, 1), 4.46 (dd, J = 6.0, 10.4, 1), 4.05 (d, J = 3.0, 1), 3.84 (dd, J = 3.3, 10.4, 1), 3.48 (dd, J = 5.8, 8.0, 1), 3.34 (dd, J = 5.2, 10.2, 1) 2.81-2.61 (m, 2), 2.65 (s, 3), 2.43 (s, 3), 2.31-2.10 (m, 2), 1.32 (d, J = 6.0, 1), 1.18 (t, J =7.1, 3); MS(ESPOS): 430.5 $[M+H]^+$ MS(ESPOS): 428.5 $[M-H]^-$.

## Example 4

### Preparation of 1-(-4-ethylpiperidyl)-N-{1- [3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-hydroxy-2-methylprop-1-yl}acetamide



[0317] Lincosamine **3b** ($R^1$=Me, $R^2$=Me) prepared by Method F (54.2 mg, 0.20 mmol) was dissolved in DMF (1.0 mL). The reaction mixture was cooled to 0°C and triethylamine (178 μL, 1.3 mmol) and BSTFA (85 μL, 0.32 mmol) were added. The reaction mixture was allowed to warm to rt, and stirred at for 1 h. 4-Ethyl pyridine-2-carboxylic acid HCl salt (Toronto) (55.3 mg, 0.29 mmol) and HATU (122 mg, 0.32 mmol) were added, and the mixture was stirred at rt for 3 h. DMF was removed and the residue was dissolved in THF (10 mL), and treated with (600 mg) Amberlite A-26 $F^-$ form resin and catalytic TBAF for 5h. The crude product was obtained by removal of the resin and evaporation of the solvent to dryness and purified by silica gel column chromatography using 10% 0.25M $NH_3$ in methanol in dichloromethane as the eluent to provide the pyridine product **11b** (m=2, $R^1$=Me, $R^2$=Me $R^3$=OH, $R^9$=ethyl) (26 mg, 33%).

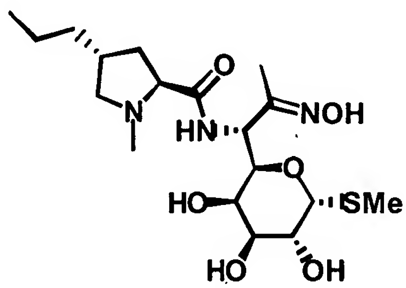
[0318] MS(ESNEG): 399.5 $[M-H]^-$.

[0319] A solution of pyridine **11b** (m=2, $R^1$=Me, $R^2$=Me $R^3$=OH, $R^9$=ethyl) (26 mg, 0.065 mmol) in 3:2 methanol:water (10 mL) was added to platinum(IV)oxide (51 mg) in a Parr bottle. Concentrated HCl (6.0 μL, 0.072 mmol) was then added. The bottle was purged and charged with $H_2$ to 65 psi and shaken for 24 h. The reaction mixture was filtered through celite and rinsed with methanol. The combined filtrate was evaporated to dryness and chromatographed on silica 80:20 dichloromethane: 0.25% ammonia in methanol to give a high $R_f$ product and the title compound (5.8 mg, 21.8%).

[0320] $^1$H NMR (300 MHz, $D_2O$) δ 5.37 (d, J = 6.0, 1), 4.41 (d, J = 9.6, 1), 4.32 (d, J = 9.3, 1), 4.08 (dd, J = 6.6, 11.0, 1), 3.93-3.90 (m, 2), 3.59 (dd, J = 3.0, 10.7, 1), 3.93-3.90 (m, 2), 3.04 (apt dt, J = 7.1, 14.6, 14.6, 1), 2.24-2.18 (m, 1), 2.20 (s, 3), 1.70-1.60 (m, 1), 1.42-1.13 (m, 1), 0.88 (dd, J =6.0, 7.4, 1); MS(ESPOS): 407.4 $[M+H]^+$.

## Example 5

### Preparation of 1-(-4-n-propyl-N-methylpyrrolidin-2-yl)-N-{1- [3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-hydroxyiminoprop-1-yl}acetamide

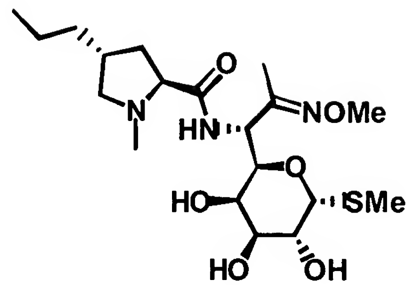



[0321] Triethylamine (0.041 mL, 0.28 mmol) and BSTFA (0.24 mL, 0.94 mmol) were added to the crude oxime **4b** ($R^1$=Me, $R^7$=H) prepared by Method G (50 mg, 0.19 mmol) in DMF (3 mL) at 0°C and the mixture was stirred at rt overnight. Next, 4-n-propylhygric acid (63 mg, 0.37 mmol) and HATU (142 mg, 0.37 mmol) were added and the mixture was stirred at rt for 4 h. DMF was removed and the residue was extracted with dichloromethane (100 mL) and washed with saturated bicarbonate (20 mL) and brine (20 mL). The residue obtained on removal of dichloromethane was then treated with 10% TFA in dichloroethane (10 mL) and dimethyl sulfide (0.5 mL) for 1 h. The solvent was then removed to obtain the crude product, which was purified by silica gel column chromatography using 20% methanol in dichloromethane as the eluent to provide the title compound (20 mg, 25%).

[0322] TLC: $R_f$ = 0.67 (20% methanol in dichloromethane); $^1$H NMR (300 MHz, $CD_3OD$) δ 0.93 (t, J = 6.8, 3), 1.31-1.44 (m, 4), 1.88 (s, 3), 1.99 (s, 3), 2.09 (m, 2), 2.11 (m, 1), 2.62-2.98 (m, 3), 2.76 (s, 3), 3.60 (m, 2), 4.10 (dd, J = 5.7, 10.20, 1), 4.27 (d, J = 9.6, 1), 5.23 (d, J = 5.5, 1), MS(ESPOS): 420 $[M+H]^+$.

## Example 6

### Preparation of 1-(-4-n-propyl-N-methylpyrrolidin-2-yl)-N-{1- [3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methoxyiminoprop-1-yl}acetamide

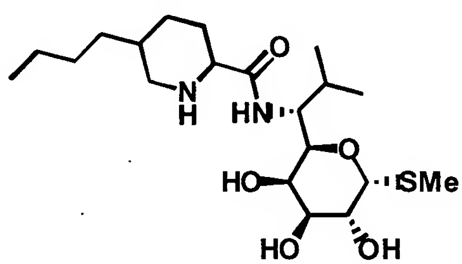


[0323] From crude oxime product **4b** prepared by Method H ($R^1$=Me, $R^7$=Me), the title compound was prepared as in Example 5 (10 mg, 47%).

[0324] TLC: $R_f$ = 0.55 (10% methanol in dichloromethane); $^1$H NMR (300 MHz, $CD_3OD$) δ 0.91 (m, 3), 1.32 (m, 4), 1.88 (s, 3), 1.98 (s, 3), 1.78-2.04 (m, 2), 2.34 (s, 3), 2.90 (dd, J = 5.1, 6.30, 8.10 1), 3.21 (dd, J = 6.3, 10.2, 1), 3.57 (dd, J = 3.3, 10.2, 1), 4.23 (dd, J = 5.4, 10.2, 1), 5.25 (d, J = 5.7, 1); MS(ESPOS): 434 $[M+H]^+$.

## Example 7

### Preparation of 1-(-3-n-butylpiperid-6-yl)-N-{1- [3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide



[0325] Lincosamine intermediate **2b** ($R^1$=Me, $R^2$=Me), prepared by Method C, was dissolved in DMF (2 mL). Triethylamine (80 mg, 1 mmol) and BSTFA (307 mg, 1.1 mmol) were added, and the mixture was stirred at rt for 1.5 h. Next, fusaric acid (143 mg, 0.7 mmol) and HATU (184 mg, 0.5 mmol) were added, and the mixture was stirred at rt for 3 h. DMF was removed and the residue was dissolved in EtOAc (50 mL), washed with sodium bicarbonate (10%, 30 mL) and brine (30 mL), and dried over sodium sulfate. The residue obtained by removing the solvent was dissolved in methanol and treated with Dowex resin $H^+$ for 1 h. The crude product obtained by filtering the resin and removing the solvent was purified on silica gel column chromatography using 10% methanol in dichloromethane as the eluent to give the title compound (100 mg, 61%).

[0326] TLC $R_f$ = 0.6 (10% methanol in dichloromethane); $^1$H NMR (300 MHz, $CD_3OD$) δ 8.47 (s, 1), 8.02 (d, J = 8.1, 1), 7.80 (d, J = 8.1, 1), 5.27 (d, J = 5.4, 1), 4.31 (m, 2), 4.12 (dd, J =

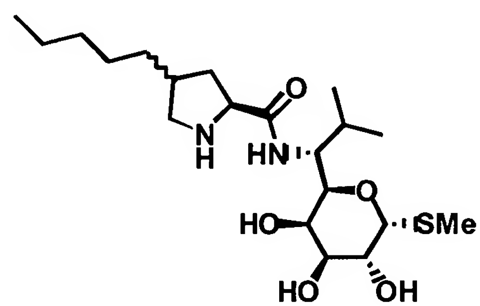
5.7, 4.2, 1), 3.85 (d, J = 3.0, 1), 3.56 (dd, J = 3.3, 6.9, 1), 2.80 (m, 2), 2.24 (m, 1), 2.11 (s, 3), 1.67 (m, 2), 1.41 (m, 2), 1.00 (m, 9); MS(ESPOS): 413 $[M+H]^+$.

**[0327]** $PtO_2$ (50 mg, 0.22 mmol) was added to compound **11b** (m=2, $R^1$=Me, $R^2$=Me, $R^3$=H, $R^9$=butyl), (70 mg, 0.16 mmol) in methanol (2 mL), water (10mL), and acetic acid (3 mL), and the mixture was hydrogenated at 50 psi overnight. The product obtained after filtering the catalyst and removing the solvent was purified on silica gel column chromatography using 30% methanol in dichloromethane as the eluent (16 mg, 46%).

**[0328]** TLC $R_f$ = 0.7 (30% methanol in dichloromethane); $^1H$ NMR (300 MHz, $CD_3OD$) δ 5.24 (d, J = 5.7, 1), 4.16 (m, 3), 3.82 (d, J = 3.3, 1), 3.53 (m, 2), 2.93 (m, 2), 2.09 (s, 3), 1.93 (m, 1), 1.76 (m, 2), 1.50 (m, 1), 1.30 (m, 7), 0.92 (m, 9); MS(ESPOS): 419 $[M+H]^+$.

## Example 8

### Preparation of 1-(4-(R,S)-n-pentylpyrrolidin-2-yl)-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide




**[0329]** Triethylamine (0.2 mL, 1.44 mmol, 3.6 equiv), followed by BSTFA (0.2 mL, 0.76 mmol, 1.9 equiv), were added to a stirred suspension of **2b** ($R^1$=Me, $R^2$=Me) prepared by Method C (100.4 mg, 0.4 mmol, 1 equiv) in anhydrous DMF (2 mL) at 0°C and under nitrogen. The resulting mixture was stirred at 0°C for 10 min, and then at rt for 50 min. The resulting solution was cooled to 0°C and a solution of **6c** ($R^9$=pentyl) (Scheme 6) prepared as described in Birkenmeyer, R. D; et al; Journal of Medicinal Chemistry **1972**, 15, 1255-1259. (144 mg, 0.51 mmol, 1.2 equiv) in anhydrous DMF (1.5 mL) was added, followed by solid HATU. The reaction mixture was allowed to warm to rt, and after 2 h, the reaction solution was evaporated to dryness under vacuum. The residual oil obtained was diluted with EtOAc (150 mL), washed sequentially with 10% citric acid (2 x 30 mL), 1:1 saturated aqueous $NaHCO_3$, water (2 x 30 mL), and brine (30 mL), dried over $Na_2SO_4$, and evaporated to dryness.

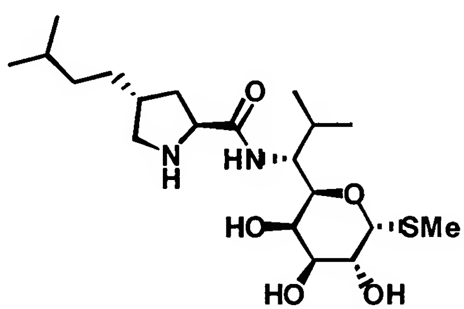
**[0330]** 1,2-Dichloroethane (8 mL), followed by dimethyl sulfide (180.3 μl), TFA (2.7 mL), and water (180.3 μl) were added to the crude product (267.5 mg) obtained above. The resulting

mixture was stirred at rt for 1h and evaporated to a minimal volume, diluted with DCE (3 x 30 mL), and evaporated to dryness. The residue obtained was purified by chromatography over silica gel, with a gradient eluent of 8-10% methanol ammonia in dichloromethane. The desired fractions were pooled together, evaporated to dryness, and lyophilized to furnish the title compound as a white fluffy powder (35.6 mg, 21.2%).

**[0331]** TLC, $R_f$= 0.15 (16% 0.25M methanolic ammonia in dichloromethane ). $^1$H NMR (300MHz, $D_2O$) δ 5.4 (d, J = 5.8, 1), 3.91(s, 1), 3.69-3.66 (m, 3), 2.1 (s, 3), 1.32-1.15 (m, 3.37), 0.93-0.87 (m, 9.8); MS(ESPOS): 419.5 $[M+H]^+$, (ESNEG): 417.45 $[M-H]^-$.

## Example 9

### Preparation of 1-[4- (3-methylbut-1-yl)pyrrolidin-2-yl]-N-{1- [3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide



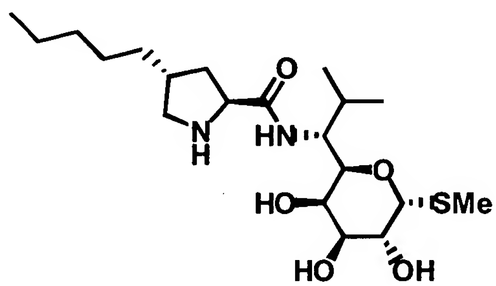

**[0332]** Triethylamine (0.13 mL, 0.96 mmol, 3.2 equiv), followed by BSTFA (0.12 mL, 0.45 mmol, 1.5 equiv), were added to a solution of **2b** ($R^1$=Me, $R^2$=Me) prepared by Method C (75 mg, 0.30 mmol, 1 equiv) in dry DMF (0.8 mL) at 0°C. The reaction mixture was stirred at 0°C for 10 min, and then at rt for 50 min. To the reaction mixture was added acid **7d** ($R^9$=2-methylbutyl), prepared by method J (160 mg, 0.56 mmol, 1.9 equiv), in a 25 mL round-bottom flask. Then HATU was added (227 mg, 0.60 mmol, 2 equiv). The reaction mixture was stirred at rt for 3 h. The reaction mixture was evaporated to dryness, taken up in ethyl acetate (100 mL), washed with 10% citric acid (2 x 60 mL), water (60 mL), half sat. $NaHCO_3$ (60 mL), and brine. The organic layer was dried over $Na_2SO_4$ and evaporated to give a yellow syrup.

**[0333]** Trifluoroacetic acid (5 mL) and water (0.33 mL) were added to a solution of the above syrup in dichloromethane (15 mL) with methyl sulfide (0.33 mL). The reaction mixture was stirred at rt for 1 h. The solvent was removed under vacuum and co-evaporated with toluene twice. The residue was purified by chromatography to provide the title compound (75 mg, 60%) as a white solid.

[0334] $^{1}$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, J = 5.4, 1), 4.18-3.99 (m, 4), 3.75 (d, J = 2.4, 1), 3.51 (dd, J = 3.3, 10.5, 1), 3.38-3.31 (m, 1), 2.68 (dd, J = 8.2, 10.6, 1), 2.23-2.05 (m, 3), 2.10 (s, 3), 1.97-1.87 (m, 1), 1.59-1.47 (m, 1), 1.46-1.34 (m, 2), 1.25-1.16 (m, 2), 0.92-0.88 (m, 12). MS(ESPOS): 419.5 $[M+H]^+$, MS(ESNEG): 417.5 $[M-H]^-$.

### Example 10

**Preparation of 1-(-4-n-pentylpyrrolidin-2-yl)-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide**



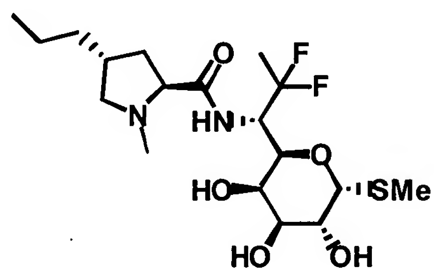
[0335] Triethylamine (0.6 mL, 4.33 mmol, 3.6 equiv), followed by BSTFA (0.6 mL, 2.27 mmol, 1.9 equiv), were added to a stirred suspension of **2b** ($R^1$=Me, $R^2$=Me) prepared by Method C (298.8 mg, 1.19 mmol, 1 equiv) in anhydrous DMF (5 mL) at 0°C and under nitrogen. The resulting mixture was stirred at 0°C for 10 min, and then at rt for 50 min. The resulting solution was cooled to 0°C and a solution of **7d** ($R^9$=n-pentyl) was prepared by Method K (400.1 mg, 1.40 mmol, 1.2 equiv) in anhydrous DMF (5 mL) was added, followed by solid HATU (678.7 mg, 1.79 mmol, 1.5 equiv). The reaction mixture was allowed to warm to rt and after 2h the reaction solution was evaporated to dryness under vacuum. The residual oil obtained was diluted with EtOAc (400 mL), washed sequentially with 10% citric acid (2 x 100 mL), 1:1 saturated aqueous $NaHCO_3$, water (2 x 100 mL), and brine (100 mL), dried over $Na_2SO_4$, and evaporated to dryness.

[0336] 1,2-Dichloroethane (35 mL), followed by dimethylsulfide (768 μL), TFA (11.5 mL), and water (768 μL) were added to the crude product (1.14 g) obtained above. The resulting mixture was stirred at rt for 1h, evaporated to a minimal volume, diluted with DCE (3 x 90 mL), and evaporated to dryness. One-third of the residue obtained was purified by chromatography over silica gel, with a gradient eluent of 8-12% methanol ammonia in dichloromethane. The desired fractions were pooled together, evaporated to dryness, treated with deuterium oxide/anhydrous acetonitrile, and lyophilized to furnish a white fluffy powder (68.2mg, 41.1%); TLC, $R_f$= 0.15 {16% 0.25M methanolic ammonia in dichloromethane}. $^{1}$H NMR (300 MHz,

$D_2O$) δ 5.41 (d, J = 5.8, 1H), 4.55 (m, 1), 4.24 (s, 2), 4.14 (m, 1), 3.91(d, J=3.3, 1), 3.70-3.66 (m, 2), 3.15 (m,1), 2.36-2.27 (m, 2), 2.19 (s, 5), 1.59-1.13 (m, 9), 0.93-0.88 (m, 9); $^{13}C$ NMR ($D_2O$,): δ 170.4, 119.4, 88.4, 70.9, 69.3, 68.8, 68.2, 60.0, 53.4, 51.4, 37.3, 36.7, 31.3, 27.9, 27.2, 22.3, 20.1, 14.8, 13.7, 13.3; MS(ESPOS):419.6$[M+H]^+$;(ESNEG):417.5$[M-H]^-$.

## Example 11

### Preparation of 1-(-4-n-propyl-N-methylpyrrolidin-2-yl)-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2,2-difluoroprop-1-yl}acetamide

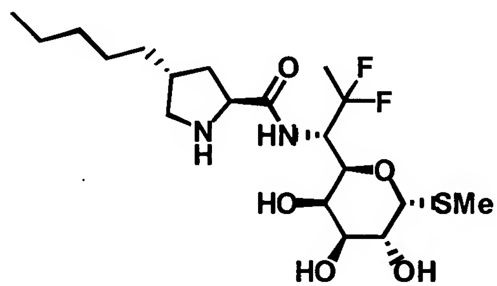


[0337] 30% Trifluoroacetic acid in dichloroethane (10 mL) and dimethylsulfide (0.5 mL) were added to lincosamine intermediate **5b** ($R^1$=Me), prepared by Method H (100 mg, 0.20 mmol). The mixture was stirred at rt for 1 h. The solvent was removed and the residue was kept under high vacuum for 1 h. N-Methyl-4-trans-propylproline (53 mg, 0.4 mmol) and HATU (114 mg, 0.30 mmol) were added to the dried compound in DMF (3 mL), and the mixture was stirred at rt overnight. DMF was removed and the residue obtained was then extracted with ethyl acetate (100 mL) and washed with saturated bicarbonate (50 mL). The organic portion was then dried using magnesium sulfate and the solvent was removed to obtain the crude product. The crude product was purified on silica gel column using ethyl acetate as the eluent (50 mg, 46%). The product (50 mg, 0.09 mmol) was then taken in methanol (2 mL) and water (1 mL), to which solid potassium carbonate (124 mg, 0.90 mmol) was added and the mixture was stirred at rt for 24 h. Solvents were then removed and the crude product was purified on silica gel column using 20% methanol in dichloromethane as the eluent (20 mg, 52%).

[0338] TLC: $R_f$ = 0.57 (20% methanol in dichloromethane); MS(ESPOS): 427 $[M+H]^+$. $^1H$ NMR (300 MHz, $CD_3OD$) δ 0.91 (m, 3), 1.34 (m, 4), 1.69 (t, J = 19.8, 3), 1.98 (s, 3), 2.20 (m, 2), 2.46 (s, 3), 3.18 (dd, J = 5.1, 10.20, 1), 3.93 (d, J = 3.0, 1), 4.08 (dd, J = 3.3, 10.20, 1), 4.40-4.70 (m, 2), 5.28 (d, J = 5.4, 1).

## Example 12

### Preparation of 1-(-4-n-pentylpyrrolidin-2-yl)-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2,2-difluoroprop-1-yl}acetamide

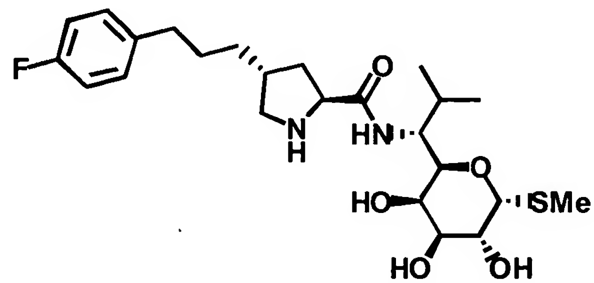


[0339] Boc 4-trans-Pentylproline **7d** ($R^9$=n-pentyl) (179 mg, 0.631 mmol), HATU (299 mg, 0.789 mmol), and diethylisopropylamine (182 mg, 1.2 mmol) were added to lincosamine intermediate **5b** ($R^1$=Me) prepared by Method H (210 mg, 0.526 mmol) in DMF (3 mL) at 0°C. The mixture was stirred at rt overnight. After removing DMF, the residue was taken in ethyl acetate and washed with saturated bicarbonate (30 mL). The organic portion was then dried over sodium sulfate and the solvent was removed to obtain the crude product. The crude product was purified by column chromatography using 30% ethyl acetate in hexanes as the eluent (200 mg, 57%). Potassium carbonate (450 mg, 3.0 mmol) was added to the product (200 mg, 0.30 mmol) of the above reaction in methanol (3 mL) and water (1 mL), and the mixture was stirred at rt for 2 h. The solvent was removed and the residue obtained was taken in 30% trifluoroacetic acid in dichloroethane (10 mL) and dimethyl sulfide (0.5 mL) and stirred for 1 h. After removing the solvent, the crude product obtained was purified by column using 10% methanol in dichloromethane as the eluent (10 mg, 90%).

[0340] TLC: $R_f$ = 0.56 (20% methanol in dichloromethane); $^1$H NMR (300 MHz, $CD_3OD$) δ 0.90 (m, 3), 1.31 (m, 7), 1.44 (m, 20), 1.73 (t, J = 19.5, 3), 2.02 (m, 1), 2.08 (s, 3), 2.24 (m, 2), 2.89 (t, J = 9.9, 1), 3.56 (m, 2), 3.86 (s, 1), 4.07 (dd, J = 6.0, 9.6, 1), 4.37 (m, 2), 4.63 (m, 1), 5.28 (d, J = 5.4, 1); MS(ESPOS): 441 $[M+H]^+$.

## Example 13

**Preparation of 1-(-4-(3-p-fluorophenyl)prop-1-ylpyrrolidin-2-yl)-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide**



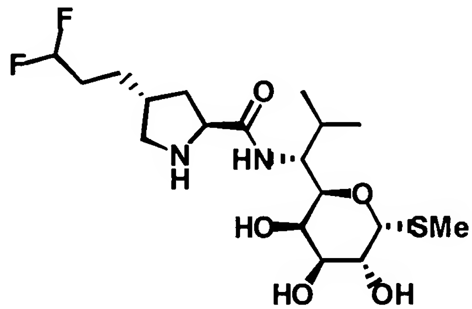
[0341] Triethylamine (0.13 mL, 0.96 mmol, 3.2 equiv), followed by BSTFA (0.12 mL, 0.45 mmol, 1.5 equiv), were added to a solution of **2b** ($R^1$=Me, $R^2$=Me) prepared by Method C (75 mg, 0.30 mmol, 1 equiv) in dry DMF (0.8 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min, and then at rt for 50 min. The reaction mixture was added to acid **8c** ($R^9$=3-(4-fluorophenyl)propyl) prepared by Method L (120 mg, 0.34 mmol, 1.1 equiv) in a 25 mL round bottom flask, followed by HATU (160 mg, 0.42 mmol, 1.4 equiv). The reaction mixture was stirred at rt for 3 h. The reaction mixture was evaporated to dryness, taken up in ethyl acetate (100 mL), and washed with 10% citric acid (2 x 60 mL), water (60 mL), half sat. $NaHCO_3$ (60 mL), and brine. The organic layer was dried over $Na_2SO_4$ and evaporated to give a yellow syrup.

[0342] Trifluoroacetic acid (5 mL) and water (0.33 mL) were added to a solution of the above syrup in dichloromethane (15 mL) with methyl sulfide (0.33 mL). The reaction mixture was stirred at rt for 1 h. The solvent was removed under vacuum and co-evaporated with toluene twice. The residue was purified by chromatography to provide 1-(2-(S)-4-(R)-(3-p-fluorophenyl)prop-1-ylpyrrolidin-2-yl)-N-{1-(S)-[2-(S)-3-(S), 4-(S), 5-(R)-trihydroxy-6-(R)-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide (90 mg, 62%) as a white solid.

[0343] $^1$H NMR (300 MHz, $CDCl_3$) δ 7.94 (brs, 1), 7.11-7.06 (m, 2), 6.97-6.90 (m, 2), 5.31 (d, J = 5.4, 1), 4.10 (dd, J = 5.7, 9.9, 1), 3.96-3.82 (m, 3), 3.68-3.52 (m, 2), 3.10-3.20 (m, 1), 2.70-2.60 (m, 1), 2.56 (dd, J = 7.4, 7.4, 2), 2.36-2.24 (m, 1), 2.13 (s, 3), 2.10-1.93 (m, 2), 1.85-1.73 (m, 1), 1.64-1.50 (m, 2), 1.40-1.30 (m, 2), 0.92-0.85 (m, 6). MS(ESPOS): 485.5 $[M+H]^+$, MS(ESNEG): 483.5 $[M-H]^-$.

## Example 14

**Preparation of 1-[2-(S)-4-(R)-(3,3-difluoroprop-1-yl)pyrrolidin-2-yl]-N-{1-[3,4,5-trihydroxy-6- (methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide**



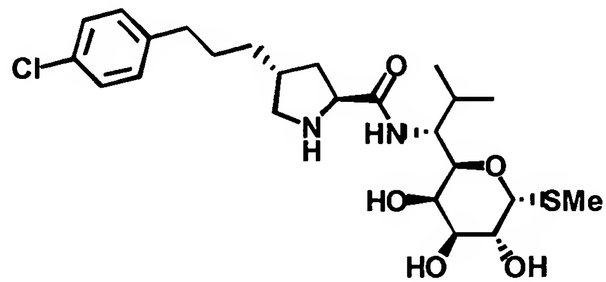
[0344] Triethylamine (0.13 mL, 0.96 mmol, 3.2 equiv), followed by BSTFA (0.12 mL, 0.45 mmol, 1.5 equiv), were added to a solution of **2b** ($R^1$=Me, $R^2$=Me) prepared by Method C (75 mg, 0.30 mmol, 1 equiv) in dry DMF (0.8 mL) at 0 °C. The reaction mixture was stirred at 0°C for 10 min, and then at rt for 50 min. The reaction mixture was added to acid **8c** ($R^9$=3,3-difluoropropyl) prepared by Method N (97 mg, 0.33 mmol, 1.1 equiv) in a 25 mL round bottom flask, followed by HATU (170 mg, 0.45 mmol, 1.5 equiv). The reaction mixture was stirred at rt for 3 h. The reaction mixture was evaporated to dryness, taken up in ethyl acetate (100 mL), and washed with 10% citric acid (2 x 60 mL), water (60 mL), half sat. $NaHCO_3$ (60 mL), and brine. The organic layer was dried over $Na_2SO_4$ and evaporated to give a yellow syrup.

[0345] Trifluoroacetic acid (5 mL) and water (0.33 mL) were added to a solution of the above syrup in dichloromethane (15 mL) with methyl sulfide (0.33 mL). The reaction mixture was stirred at rt for 1 h. The solvent was removed under vacuum and co-evaporated with toluene twice. The residue was purified by chromatography to provide 1-[2-(S)-4-(R)-(3,3-difluoroprop-1-yl)pyrrolidin-2-yl]-N-{1-[3,4,5-trihydroxy-6- (methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide (81 mg, 64%) as a white solid.

[0346] $^1$H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 8.1, 1), 5.80 (dddd, J = 4.2, 4.2, 57, 57, 1), 5.31 (d, J = 5.7, 1), 4.11 (dd, J = 5.4, 9.9, 1), 3.96-3.82 (m, 3), 3.64-3.52 (m, 2), 3.23-3.10 (m, 1), 2.73-2.60 (m, 1), 2.36-2.23 (m, 1), 2.13 (s, 3), 2.18-1.95 (m, 2), 1.90-1.73 (m, 3), 1.56-1.43 (m, 2), 0.93-0.85 (m, 6). MS(ESPOS): 427.5 $[M+H]^+$, MS(ESNEG): 425.5 $[M-H]^-$.

## Example 15

**Preparation of 1-(-4-(3-p-chlorophenyl)prop-1-ylpyrrolidin-2-yl)-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide**



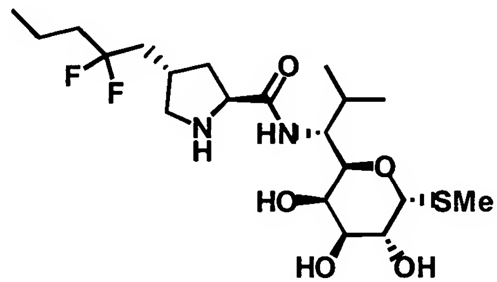
[0347] Triethylamine (88.3 µL, 0.64 mmol, 3.2 equiv), followed by BSTFA (79.2 mL, 0.30 mmol, 1.5 equiv), were added to a solution of **2b** ($R^1$=Me, $R^2$=Me) prepared by Method C (50 mg, 0.20 mmol, 1 equiv) in dry DMF (0.5 mL) at 0°C. The reaction mixture was stirred at 0°C for 10 min, and then at rt for 50 min. The reaction mixture was added to **8c** ($R^9$=3-(4-chlorophenyl)propyl) prepared by Method M (97.3 mg, 0.26 mmol, 1.3 equiv) in a 25 mL round bottom flask, followed by HATU (123 mg, 0.32 mmol, 1.6 equiv). The reaction mixture was stirred at rt for 3 h. The reaction mixture was evaporated to dryness, taken up in ethyl acetate (60 mL), and washed with 10% citric acid (2 x 40 mL), water (40 mL), half sat. $NaHCO_3$ (40 mL), and brine. The organic layer was dried over $Na_2SO_4$ and evaporated to give a yellow syrup.

[0348] Trifluoroacetic acid (3 mL) and water (0.2 mL) were added to a solution of the above syrup in dichloromethane (9 mL) with methyl sulfide (0.2 mL). The reaction mixture was stirred at rt for 1 h. The solvent was removed under vacuum and co-evaporated with toluene twice. The residue was purified by chromatography to provide 1-(2-(S)-4-(R)-(3-p-chlorophenyl)prop-1-ylpyrrolidin-2-yl)-N-{1-(S)-[2-(S)-3-(S), 4-(S), 5-(R)-trihydroxy-6-(R)-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide (41.6 mg, 42%) as a white solid.

[0349] $^1$H NMR (300 MHz, $CDCl_3$) δ 7.26-7.21 (m, 2), 7.17-7.12 (m, 2), 5.23 (d, J = 5.7, 1), 4.10-4.00 (m, 3), 3.83-3.75 (m, 1), 3.74-3.70 (m, 1), 3.54-3.48 (m, 1), 3.25-3.18 (m, 1), 2.63-2.50 (m, 3), 2.20-2.00 (m, 3), 2.09 (s, 3), 1.85-1.74 (m, 1), 1.68-1.55 (m, 2), 1.42-1.33 (m, 2), 0.95-0.85 (m, 6). MS(ESPOS): 501.5 $[M+H]^+$ MS(ESNEG): 499.4 $[M-H]^-$.

## Example 16

**Preparation of 1-[2-(S)-4-(S)-(2,2-difluoropent-1-yl)pyrrolidin-2-yl]-N-{1-[3,4,5-trihydroxy-6- (methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide**



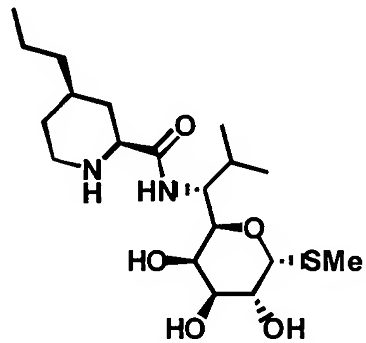
[0350] Triethylamine (88.3 mL, 0.64 mmol, 3.2 equiv), followed by BSTFA (79.2 mL, 0.30 mmol, 1.5 equiv), were added to a solution of **2b** ($R^1$=Me, $R^2$=Me) prepared by Method C (50 mg, 0.20 mmol, 1 equiv) in dry DMF (0.5 mL) at 0°C. The reaction mixture was stirred at 0°C for 10 min, and then at rt for 50 min. The reaction mixture was added to the acid **9d** ($R^9$=2,2-difluoropentyl) prepared by Method O (67.7 mg, 0.21 mmol, 1.1 equiv) in a 25 mL round bottom flask, followed by HATU (101 mg, 0.27 mmol, 1.3 equiv). The reaction mixture was stirred at rt for 3h. The reaction mixture was evaporated to dryness, taken up in ethyl acetate (60 mL), and washed with 10% citric acid (2 x 40 mL), water (40 mL), half sat. $NaHCO_3$ (40 mL), and brine. The organic layer was dried over $Na_2SO_4$ and evaporated to give a yellow syrup.

[0351] Trifluoroacetic acid (3 mL) and water (0.20 mL) were added to a solution of the above syrup in dichloromethane (9 mL) with methyl sulfide (0.20 mL). The reaction mixture was stirred at rt for 1 h. The solvent was removed under vacuum and co-evaporated with toluene twice. The residue was purified by chromatography to provide 1-[2-(S)-4-(S)-(2,2-difluoropent-1-yl)pyrrolidin-2-yl]-N-{1-[3,4,5-trihydroxy-6- (methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide (56 mg, 62%) as a white solid.

[0352] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, J = 5.7, 1), 4.17-4.04 (m, 3), 3.98 (dd, J = 3.3, 9.3, 1), 3.77 (d, J = 3, 1), 3.51 (dd, J = 3.4, 10.3, 1), 3.40 (dd, J = 6.9, 10.5, 1), 2.71 (dd, J = 10.2, 10.2, 1), 2.42-2.33 (m, 1), 2.23-2.11 (m, 2), 2.10 (s, 3), 2.08-1.73 (m, 5), 1.56-1.42 (m, 2), 0.99-0.89 (m, 9). MS(ESPOS): 455.5 $[M+H]^+$; MS(ESNEG): 453.5 $[M-H]^-$.

## Example 17

### Preparation of 1-(-4-n-propylpiperid-6-yl)-N-{1- [3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide



[0353] Triethylamine (0.18 mL, 1.26 mmol) and BSTFA (0.549 mL, 2.1 mmol) were added to the lincosamine intermediate **2b** ($R^1$=Me, $R^2$=Me) prepared by Method D (102 mg, 0.42 mmol) in DMF (5 mL) at 0°C, and the mixture was stirred at rt for 3 h. Acid **10b** ($R^9$=propyl) prepared by Method P (200 mg, 0.84 mmol) and HATU (319 mg, 0.84 mmol) were added and the mixture was stirred for 4 h at rt. DMF was removed and the residue was extracted with ethyl acetate (100 mL) and washed with saturated bicarbonate (40 mL). The product obtained by removal of solvent was taken up in methanol and treated with Dowex $H^+$ resin for 1 h. After filtering the resin, methanol was removed to obtain the crude product. The crude product was then purified on silica gel column using 10% methanol in dichloromethane as the eluent to provide pyridine **11b** ($R^1$=Me, $R^2$=Me, $R^3$=H, $R^9$=propyl) (117 mg, 58%).

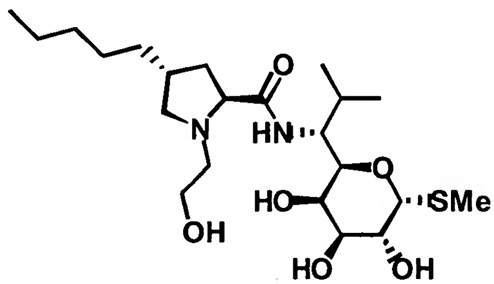
[0354] TLC: $R_f$ = 0.81 (10% methanol in dichloromethane); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, J = 6.3, 6H), 2.19 (m, 2), 2.32 (s, 3), 2.43 (m, 1), 2.84-2.97 (m, 4), 3.74 (m, 1), 4.06 (m, 1), 4.31 (m, 1), 4.52 (m, 2), 5.42 (d, J = 5.7, 1), 7.33-7.61 (m, 5), 7.80 (m, 1), 8.15 (s, 1), 8.69 (d, J = 4.8, 1); MS (ESPOS): 475 $[M+H]^+$.

[0355] $PtO_2$ (100 mg, 0.44 mmol) was added to pyridine **11b** ($R^1$=Me, $R^2$=Me, $R^3$=H, $R^9$=propyl), (150 mg, 0.37 mmol) in methanol (2 mL), water (10mL), and acetic acid (3 mL), and the mixture was hydrogenated at 50 psi overnight. The product obtained after filtering the catalyst and removing the solvent was purified by silica gel column chromatography using 30% methanol in dichloromethane as the eluent to provide the title compound (20 mg, 14%).

[0356] TLC: $R_f$ = 0.7 (50% methanol in dichloromethane); $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, J = 6.9, 1), 4.86 (m, 1), 4.13 (m, 2), 3.79 (d, J = 3.3, 1), 3.52 (dd, J = 3.3, 9.9, 1), 3.32 (m, 1), 3.17 (m, 1), 2.67 (m, 1), 2.17 (m, 1), 2.10 (s, 3), 1.97 (m, 1), 1.74 (m, 1), 1.54 (m, 1), 1.38 (m, 2), 1.31 (m, 2), 1.14 (m, 2), 1.02 (m, 9) MS(ESPOS): 405 $[M+H]^+$.

## Example 18

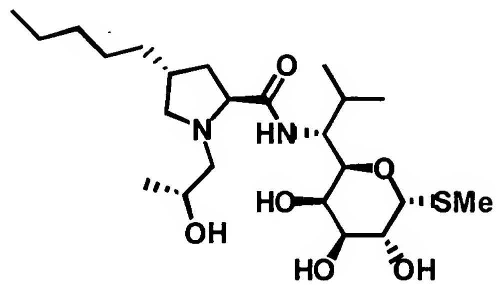
**Preparation of 1-[2-(S)-4-(R)-n-pentyl-N-(2-hydroxyeth-1-yl)pyrrolidin-2-yl]-N-{1-[3,4,5-trihydroxy-6- (methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide**



[0357] DIEA (0.1 mL, 0.57 mmol) and liquid ethylene oxide (3 mL) were added to a stirred solution of crude 1-(-4-n-pentylpyrrolidin-2-yl)-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide, prepared as in Example 10 (237.4 mg), in anhydrous methanol (10 mL), at 0°C and under nitrogen. The resulting solution was stirred at -4°C for 18 h and evaporated to dryness. The residue obtained was purified by chromatography over silica gel with an eluent of 5% methanol ammonia in dichloromethane. The desired fractions were evaporated and lyophilized (deuterium oxide/anhydrous acetonitrile, 1:1, v/v, 10mL) to furnish the title compound as a fluffy white powder (50.1mg, 30.2%); TLC, $R_f$= 0.68 (14% methanolic ammonia in dichloromethane); $^1$H NMR (300 MHz) δ 5.40 (d, J=5.8, 1), 4.55 (m, 1), 4.24 (s, 1), 4.17-4.11 (m, 1), 3.99-3.89 (m, 4), 3.69-3.65 (m, 1), 3.47 (d, J=4.4, 2), 3.01 (m, 1), 2.33 (br s,4), 2.18 (s,4), 1.57-1.32 (m,9), 0.94-0.87 (m, 9). MS(ESPOS):464$[M+H]^+$;(ESNEG):497.5[M-H+HCl].

## Example 19

**Preparation of 1-[2-(S)-4-(R)-n-pentyl-N-(2-(R)-methyl-2-hydroxyeth-1-yl)pyrrolidin-2-yl]-N-{1-[3,4,5-trihydroxy-6- (methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide**

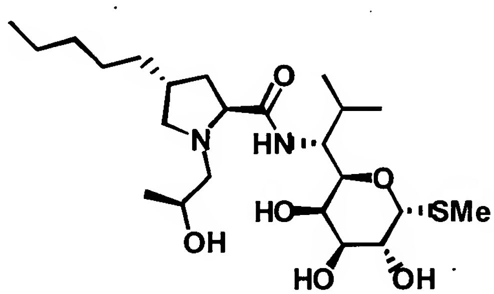


[0358] DIEA (0.1mL, 0.58 mmol, 1 equiv) and R(+)-propylene oxide (3 mL) were added to a stirred cool solution of crude 1-(2-(S)-4-(R)-n-pentylpyrrolidin-2-yl)-N-{1-[3,4,5-trihydroxy-6- (methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide (307.6 mg, 0.58 mmol, 1 equiv), prepared as in Example 10, in anhydrous methanol (10mL), at 0°C and under nitrogen. The resulting solution was stirred at -4°C for 18 h and evaporated to dryness. The residue obtained was purified by chromatography over silica gel, with an eluent of 6% methanol ammonia in dichloromethane. The desired fractions were evaporated, and lyophilized (deuterium oxide/anhydrous acetonitrile, 1:1, v/v, 20mL) to furnish the title compound as a fluffy white powder (91mg, 48%).

[0359] TLC, $R_f = 0.7$ (14% methanolic ammonia in dichloromethane); $^1H$ NMR(300 MHz, $CD_3OD$) δ 5.44 (d, J = 5.5, 1), 4.31 (s, 2), 4.26-4.11 (m, 1), 3.97 (d, J = 3.3,1.1,1), 3.75 (dd, J = 3.3,3.3, 1), 3.39 (dd, J = 3.8,3.8, 1), 2.31 (s, 3), 1.5-0.95 (m, 12), 1.34 (d, J = 6.0, 4), 1.17-1.10 (m, 13); MS(ESPOS): 477.6 $[M+H]^+$, (ESNEG): 475.6 $[M-H]^-$.

## Example 20

**Preparation of 1-[2-(S)-4-(R)-n-pentyl-N-(2-(S)-methyl-2-hydroxyeth-1-yl)pyrrolidin-2-yl]-N-{1-[3,4,5-trihydroxy-6- (methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide**



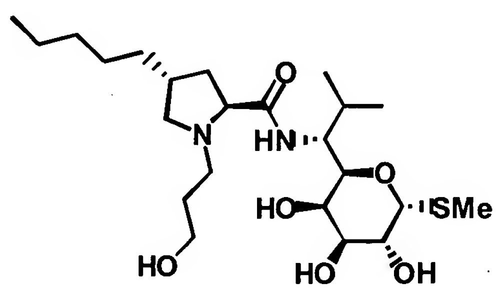
[0360] Dimethyl sulfide (62 μL), TFA (1 mL), and water (62 μL) were added to a stirred solution of the Boc-protected 1-(2-(S)-4-(R)-n-pentylpyrrolidin-2-yl)-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide (92mg, 0.18 mmol), prepared as in Example 10, in anhydrous dichloroethane (3 mL). The resulting solution was stirred at rt

for 1 h and evaporated to dryness. Anhydrous methanol (8 mL) and DIEA (31 $\mu$L, 0.18 mmol) were added to the residue obtained. The mixture was cooled to -4°C and S-(-)-propylene oxide (2 mL) was added. The resulting solution was stirred at -4°C for 18 h, evaporated to dryness, and purified by chromatography over silica gel, with an eluent of 6% methanol ammonia in dichloromethane. The desired fractions were evaporated and lyophilized (deuterium/anhydrous acetonitrile, 1:1, v/v, 8 mL) to furnish the title compound as a fluffy white powder (29.8 mg, 31.2%).

**[0361]** TLC, $R_f$ = 0.7 (12% methanolic ammonia in dichloromethane); 1H NMR (300 MHz, $CD_3OD$) δ 5.44 (d, J = 5.5,1), 4.35-4.19 (m, 4), 4.02 (d, J = 3.3, 2), 2.75 (d, J = 6.3,2.2, 3), 2.3 (s, 3), 1.50 (m, 11), 1.4 (d, J = 6.0, 3.5, 3), 1.16-1.10 (m, 12). MS(ESPOS): 477.6 $[M+H]^+$; (ESNEG) 475.4 $[M-H]^-$.

### Example 21

### Preparation of 1-(-4-n-pentyl-N-(3-hydroxyprop-1-yl)pyrrolidin-2-yl)-N-{1-[3,4,5-trihydroxy-6- (methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide

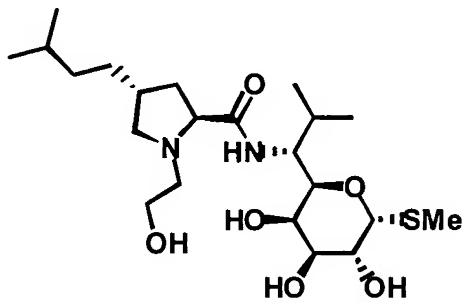



**[0362]** Triethylamine (0.2 mL, 1.38 mmol, 3 equiv), followed by 3-bromo-1-propanol (60 $\mu$L, 0.69 mmol, 1.5 equiv), were added to a stirred solution of crude 1-(2-(S)-4-(R)-n-pentylpyrrolidin-2-yl)-N-{1-(R)- [2-(S)-3-(S), 4-(S), 5-(R)-trihydroxy-6-(R)-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide (192.5 mg, 0.46 mmol, 1 equiv), prepared as in Example 10, in anhydrous acetonitrile (2 mL), under nitrogen. The resulting mixture was stirred at rt for 18 h and evaporated to dryness. The residue obtained was purified by chromatography over silica gel with an eluent of 5% methanol ammonia in dichloromethane. The desired fractions were pooled together, evaporated to dryness, and lyophilized to furnish the title compound as a white fluffy powder (13.5 mg, 6%).

**[0363]** TLC, $R_f$= 0.75 (14% methanolic ammonia in dichloromethane); $^1$H NMR (300 MHz, $CD_3OD$) δ 5.44 (d, J = 5.8, 1), 4.33-4.26 (m, 4), 4.01 (d, J = 2.7, 1), 3.85-3.74 (m, 6), 2.29 (s, 3), 2.1 (m, 4), 1.54 (m, 8), 1.16-1.08 (m, 12); MS (ESPOS): 477.6 $[M+H]^+$.

## Example 22

**Preparation of 1-[2-(S)-4-(R)-(3-methylbut-1-yl)-N-(2-hydroxyeth-1-yl)pyrrolidin-2-yl]-N-{1-[3,4,5-trihydroxy-6- (methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide**

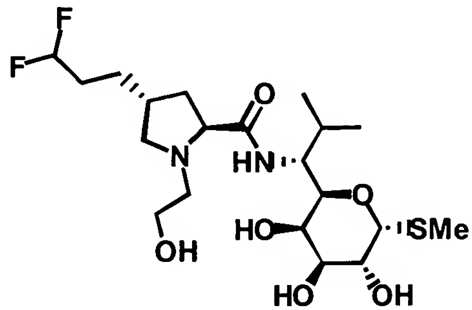


[0364] Ethylene oxide (0.6 mL) was added to a solution of 1-[2-(S)-4-(R)-(3-methylbut-1-yl)pyrrolidin-2-yl]-N-{1-(R)- [2-(S)-3-(S), 4-(S), 5-(R)-trihydroxy-6-(R)-(methylthio)-tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide (35.1 mg, 0.084 mmol), prepared as in Example 9, in methanol (3 mL), at 0°C. The reaction mixture was stirred at 4°C overnight. Additional ethylene oxide (0.6 mL) was added and stirred at 4°C overnight. The reaction mixture was concentrated and purified by chromatography to give a white solid, 1-[2-(S)-4-(R)-(3-methylbut-1-yl)-N-(2-hydroxyeth-1-yl)pyrrolidin-2-yl]-N-{1-(R)- [2-(S)-3-(S), 4-(S), 5-(R)-trihydroxy-6-(R)-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide (24.1 mg, 62%).

[0365] $^1$H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 9.0, 1), 5.32 (d, J = 5.4, 1), 5.24 (d, J = 3.0, 1), 4.13-4.07 (m, 1), 4.01 (ddd, J = 2.8, 9.9, 9.9, 1), 3.86 (d, J = 10.8, 1), 3.78-3.68 (m, 2), 3.61-3.57 (m, 1), 3.56-3.48 (m, 1), 3.36-3.32 (m, 1), 3.27-3.21 (m, 1), 2.94-2.85 (m, 1), 2.76-2.70 (m, 1), 2.55 (ddd, J = 3.6, 3.6, 12.6, 1), 2.41-2.37 (m, 1), 2.36-2.27 (m, 1), 2.15 (s, 3), 2.03-1.95 (m, 2), 1.93-1.81 (m, 1), 1.54-1.42 (m, 1), 1.39-1.26 (m, 2), 1.22-1.10 (m, 2), 0.99-0.92 (m, 6), 0.90-0.84 (m, 6). MS(ESPOS): 463.5 $[M+H]^+$ MS(ESNEG): 461.5 $[M-H]^-$.

## Example 23

**Preparation of 1-[4- (3,3-difluoroprop-1-yl)-N-(2-hydroxyeth-1-yl)pyrrolidin-2-yl]-N-{1-[3,4,5-trihydroxy-6- (methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide**



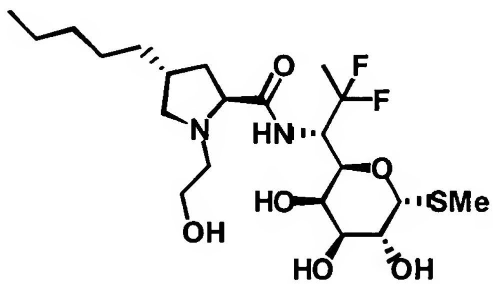
[0366] Ethylene oxide (0.4 mL) was added to a solution of 1-[2-(S)-4-(R)-(3,3-difluoroprop-1-yl)pyrrolidin-2-yl]-N-{1-(R)- [2-(S)-3-(S), 4-(S), 5-(R)-trihydroxy-6-(R)-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide, prepared as in Example 14 (29.7 mg, 0.07 mmol), in methanol (2 mL), at 0°C. The reaction mixture was stirred at 4°C overnight. Additional ethylene oxide (0.4 mL) was added and stirred at 4°C overnight. The reaction mixture was concentrated and purified by chromatography to give a white solid, 1-[2-(S)-4-(R)-(3-methylbut-1-yl)-N-(2-hydroxyeth-1-yl)pyrrolidin-2-yl]-N-{1-(R)- [2-(S)-3-(S), 4-(S), 5-(R)-trihydroxy-6-(R)-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide (19.3 mg, 59%).

[0367] $^1$H NMR (300 MHz, $CDCl_3$) δ 5.86 (dddd, J = 4.3, 4.3, 57, 57, 1), 5.23 (d, J = 5.7, 1), 4.13-4.04 (m, 3), 3.75 (d, J = 3.3, 1), 3.73-3.57 (m, 2), 3.53 (dd, J = 3.3, 10.2, 1), 3.42-3.36 (m, 1), 3.26-3.18 (m, 1), 2.88-2.78 (m, 1), 2.62-2.55 (m, 1), 2.17-2.00 (m, 4), 2.10 (s, 3), 1.94-1.73 (m, 3), 1.55-1.45 (m, 2), 0.98-0.91 (m, 6).

MS (ESPOS): 471.5 $[M+H]^+$, MS (ESNEG): 469.4 $[M-H]^-$.

## Example 24

**Preparation of 1-[2-(S)-4-(R)-n-pentyl-N-(2-hydroxyeth-1-yl)pyrrolidin-2-yl]-N-{1-[3,4,5-trihydroxy-6- (methylthio)tetrahydropyran-2-yl]-2,2-difluoroprop-1-yl}acetamide**

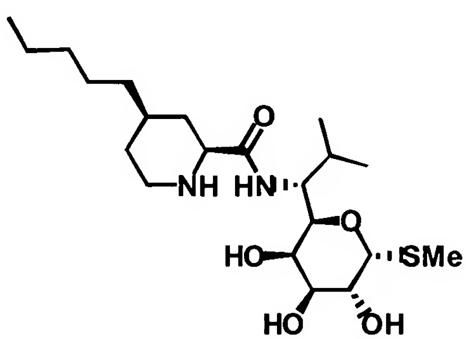


[0368] Ethylene oxide (1 mL, excess) was added to the title compound from Example 12 (60 mg, 0.136 mmol) in methanol (5 mL) at 0°C, and the mixture was stirred at 4°C overnight. The solvent was removed and the crude product was purified by silica gel column chromatography using 10% methanol in dichloromethane as the eluent (25 mg, 38%).

[0369] TLC: $R_f = 0.76$ (5% methanol in dichloromethane); $^1H$ NMR (300 MHz, $CD_3OD$) δ 0.89 (m, 3), 1.30 (m, 8), 1.68 (t, J = 19.4, 3), 1.78 (m, 1), 1.99 (m, 2), 2.07 (s, 3), 2.63 (m, 1), 2.73 (m, 1), 3.19 (m, 1), 3.58 (m, 3), 3.95 (m, 1), 4.08 (dd, J = 6.0, 9.90, 1), 4.44-4.60 (m, 2), 5.26 (d, J = 5.4, 1); MS (ESPOS): 485 $[M+H]^+$.

## Example 25

**Preparation of 1-(4-n-pentylpiperid-6-yl)-N-{ [3, 4, 5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide**



[0370] 4-Pentylpyridine-2-carboxylic acid **(10b)** ($R^9$=pentyl) was made by employing Method P. To 4-pentylpyridine (3 g, 20 mmol) in acetic acid (30 mL), hydrogen peroxide (0.7 g, 30%, 20 mmol) was added and refluxed overnight. Removal of solvent resulted in residue which was dissolved in DCM (100 mL) dried over $MgSO_4$ and filtered. Removal of DCM resulted in a

brown liquid, 4-pentylpyridine-N-oxide, (3.3 g, 100%). To trimethylsilyl cyanide (2.37 g, 24 mmol), 4-pentylpyridine N-oxide (3.3 g, 20 mmol) in DCM (10 mL) was added followed by dropwise addition of dimethylcarbamoyl chloride (2.56 g, 24 mmol) in DCM (10 mL). After stirring at room temperature overnight, sodium bicarbonate (100 mL, 10 %) was added and the organic layer was separated. The aqueous layer was extracted twice with DCM (50 mL) and the combined organic layer was dried over magnesium sulfate. Removal of solvent resulted in compound **10a** ($R^9$=pentyl) (4.1 g, 100%).

[0371] $^1$H NMR (300 MHz, $CD_3OD$) δ 8.52 (m, 1), 7.46 (s, 1), 7.27 (m, 1), 3.00 (m, 2), 2.60 (m, 2), 1.60 (m, 2), 1.27 (m, 2), 0.86 (m, 3). MS (ESPOS): 175 $[M+H]^+$.

[0372] The 4-Pentyl-2-cyanopyridine (**10a**) ($R^9$=pentyl) (3.4 g, 19.5 mmol) from the previous step was dissolved in HCl (6 N, 100 mL) and refluxed overnight. The residue obtained on removal of HCl was purified by column chromatography using 20% MeOH in DCM (3.7 g, 100%) to give product compound **10(b)**. $^1$H NMR (300 MHz, $CD_3OD$) δ 8.74 (d, J=6.3, 1), 8.39 (s, 1), 8.06 (d, J=6.3, 1), 2.98 (t, J=7.2, 2), 1.77(m, 2), 1.39 (m, 4), 0.95 (t, J=7.2, 3H). MS (ESNEG): 192 $[M-H]^-$.

[0373] Then to 7-methyl α-thiolincosaminide **2b** ($R^1$=Me, $R^2$=Me) (90 mg, 0.35 mmol) in DMF (2ml), TEA (72 mg, 0.7 mmol), BSTFA (276 mg, 1.05 mmol) were added at 0 °C and stirred at room temperature for 1.5 hr. Then the acid (**10b**) ($R^9$=pentyl) (138 mg, 0.7 mmol) and HATU (165 mg, 0.53 mmol) was added to the reaction mixture, and stirred at room temperature overnight. DMF was completely removed, the residue was taken up in EtOAc (50 mL), washed with sodium bicarbonate (10%, 50 mL), brine (50 mL). The product obtained after drying over magnesium sulfate and concentration was taken up in methanol (10 mL) and treated with NR-50 resin (150 mg) for 3 hr. The resin was filtered and the solvent was removed. Purification of the crude product was carried out silica gel column chromatography using 3% MeOH in DCM as eluent to obtain compound **11b** ($R^1$=Me, $R^2$=Me $R^3$=H, $R^9$=pentyl) (90 mg, 59%):

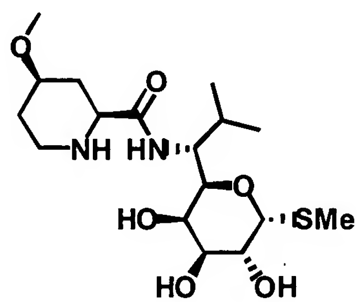
[0374] $^1$H NMR (300 MHz, $CD_3OD$) δ 8.50 (d, J=5.1, 1), 7.95 (s, 1), 7.11 (m, 1), 5.25 (d, J=5.7, 1), 4.20-4.87 (m, 3), 3.85 (d, J=3.3, 1), 3.55 (dd, J=3.3, 7.2, 1), 2.72 (m, 2), 2.16 (m, 4), 1.67 (m, 2), 1.35 (m, 4), 0.96 (m, 9). MS (ESPOS): 427 $[M+H]^+$.

[0375] To pyridine **11b** ($R^1$=Me, $R^2$=Me $R^3$=H, $R^9$=pentyl) (90 mg, 0.7 mmol) in water (10 mL), AcOH (3 mL) and MeOH (2 mL), $PtO_2$ (100 mg) was added, hydrogenated at 55 psi overnight. The solvent was removed to obtain the crude product. Purification of the crude product was carried out by silica gel column chromatography using 20% MeOH in DCM to obtain the title compound (35 mg, 38%).

[0376] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.23 (d, J=5.1, 1), 4.17 (m, 3), 3.79 (d, J=3.3, 1), 3.52 (m, 1), 3.38 (m, 1), 3.07 (m, 1), 2.68 (m, 1), 2.14 (m, 4), 1.88 (m, 1), 1.71 (m, 1), 1.52 (m, 1), 1.30 (m, 8), 1.07 (m, 3), 0.90 (m, 9); MS (ESPOS): 433 $[M+H]^+$.

## Example 26

### Preparation of 1-(4-methoxypiperid-6-yl)-N-{ [3, 4, 5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide




[0377] 4-Methoxypyridine-2-carboxylic acid, compound **10(b)** ($R^9$ = methoxy), was made employing Method P. To trimethylsilyl cyanide (0.95 g, 9.6 mmol), 4-methoxypyridine N-oxide (1 g, 8 mmol) in DCM (10 mL) was added, followed by dimethylcarbamoyl chloride (1.03 g, 9.6 mmol) in DCM (10 mL), dropwise. After stirring at room temperature overnight, sodium bicarbonate (100 mL, 10%) was added, and the organic layer was separated. The aqueous layer was extracted twice by DCM (50 mL each). The combined organic layer was dried over magnesium sulfate and the solvent was removed to obtain product, compound **10a** (0.97 g, 90%):

[0378] $^1$H NMR (300 MHz, $CD_3OD$) δ 8.52 (m, 1), 7.22 (m, 1), 7.01 (m, 1), 3.92 (s, 3H); MS (ESPOS): 135 $[M+H]^+$.

[0379] 4-Methoxy-2-cyanopyridine, compound **10a** ($R^9$ = methoxy), (0.97 g, 7.2 mmol) was dissolved in HCl (6N, 50 mL), and refluxed overnight. The HCl was evaporated and the resulting product was crystallized from acetonile, to give compound **10b** ($R^9$=methoxy) (0.6 g, 60%).

[0380] $^1$H NMR (300 MHz, $CD_3OD$) δ 8.65 (m, 1), 7.99 (m, 1), 7.68 (m, 1), 4.21 (s, 3H). MS (ESNEG): 152 $[M-H]^-$.

**[0381]** To 7-methyl α-thiolincosaminide, compound **2b** ($R^1$=Me, $R^2$=Me), (90 mg, 0.35 mmol) in DMF (2 mL), TEA (72 mg, 0.7 mmol), BSTFA (276 mg, 1.05 mmol) were added at 0°C and left stirred at room temperature for 1.5 hr. Then compound **10b** ($R^9$ = methoxy) (109 mg, 0.7 mmol) and HATU (165 mg, 0.53 mmol) were added to the reaction mixture, and stirred at room temperature overnight. The DMF was completely removed and the residue was taken up in EtOAc (50 mL), washed with sodium bicarbonate (10%, 30 mL), brine (30 mL), and dried over magnesium sulfate. The solvent was removed to obtain a brown oil-like liquid, which was dissolved in methanol (10 mL) and treated with NR-50 resin for 1 hr. The resin was filtered, and the solvent was removed to obtain the crude material. Purification was carried out on silica gel column chromatography using EtOAc as eluent to obtain compound **11b** ($R^1$=Me, $R^2$=Me $R^3$=H, $R^9$=methoxy) (100 mg, 72%).

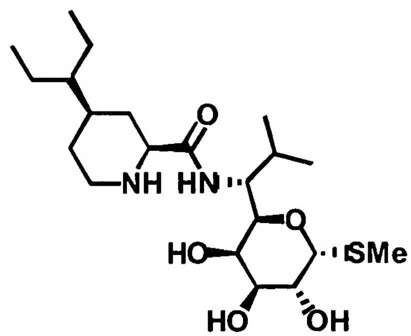
**[0382]** $^1$H NMR (300 MHz, $CD_3OD$) δ 8.42 (m, 1), 7.64 (m, 1), 7.07 (m, 1), 5.25 (d, J=5.4, 1), 4.07-4.87 (m, 3), 3.94 (m, 4), 3.56 (m, 1), 2.99 (m, 2), 2.80 (m, 1), 2.22 (m, 1), 2.11 (s, 3), 0.96 (m, 3). MS (ESPOS): 387 $[M+H]^+$.

**[0383]** To compound **11b** ($R^1$=Me, $R^2$=Me $R^3$=H, $R^9$=methoxy) (100 mg, 0.26 mmol) in water (10 mL), AcOH (3 mL) and MeOH (2 mL), $PtO_2$ (100 mg) were added and hydrogenated at 55 psi overnight. The solvent was removed to obtain the crude product. Purification of the crude product was carried out by silica gel column chromatography using 20 % MeOH in DCM to obtain the title compound. (9 mg, 9%).

**[0384]** $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, J=5.7, 1), 4.17 (dd, J=9.9; 3.3, 1), 4.07 (m, 2), 3.79 (m, 1), 3.52 (dd, J=10.5; 3.3, 1), 3.35 (s, 3), 3.18 (m, 2), 2.72 (m, 1), 2.16 (m, 1), 2.12 (s, 3) 1.99 (m, 2), 1.50 (m, 1), 1.24 (m, 2), 0.90 (d, J=6.9, 6); MS (ESPOS): 393 $[M+H]^+$.

## Example 27

### Preparation of 1-[4-(1-ethylprop-1-yl)piperid-6-yl]-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide



[0385] 4-Isopentylpyridine-2-carboxylic acid, compound **10b** ($R^9$ = 1-ethyl-propyl), was made by employing Method P. To 4-(1-ethyl-propyl)-pyridine (8.5 g, 57 mmol) in acetic acid (30 mL), hydrogen peroxide (17.8 g, 30 %, 57 mmol) was added. The resulting reaction mixture was refluxed overnight. The residue obtained on removal of solvent was dissolved in DCM (100 mL), dried over $MgSO_4$. After filtering, the solvent was removed to obtain a brown liquid, 4-(1-ethyl-propyl)-pyridine-N-oxide (9 g, 95%).

[0386] To a solution of trimethylsilyl cyanide (6.5 g, 65 mmol) and 4-(1-ethyl-propyl)-pyridine-N-oxide (9 g, 54 mmol) in DCM (25 mL) was added a solution of dimethylcarbamoyl chloride (7 g, 65 mmol) in DCM (10 mL), dropwise. After stirring at room temperature overnight, sodium bicarbonate (100 mL, 10%) was added, and the organic layer was separated. The aqueous layer was extracted twice with DCM (50 mL). The combined organic layer was dried over magnesium sulfate and the solvent was removed to obtain the product, compound **10a** ($R^9$ = 1-ethyl-propyl) (9.6 g, 100%).

[0387] $^1$H NMR (300 MHz, $CD_3OD$) δ 8.58 (m, 1), 7.46 (m, 1), 7.26 (m, 1), 2.42 (m, 1), 1.77 (m, 4)), 0.78 (t, J=7.5, 6). MS (ESPOS): 175 $[M+H]^+$.

[0388] Compound **10a** ($R^9$ = 1-ethyl-propyl) (9.5 g, 54 mmol) was dissolved in HCl (6N, 50 mL) and refluxed overnight. HCl was evaporated and the resulting product, compound **10b** ($R^9$ = 1-ethyl-propyl), was crystallized from acetonitrile (10 g, 100%).

[0389] $^1$H NMR (300 MHz, $CD_3OD$) δ 8.86 (m, 1), 8.45 (m, 1), 8.20 (m, 1), 2.92 (m, 1), 1.87 (m, 4), 0.84 (t, J=7.5, 6). MS (ESNEG): 192 $[M-H]^-$.

[0390] To the acid **10b** (77 mg, 0.4 mmol) in DMF (2 mL), 7-methyl α-thiolincosaminide, compound **2b** ($R^1$=Me, $R^2$=Me), (100 mg, 0.4 mmol) was added, followed by HBTU (166 mg, 0.44 mmol) and DIEA (205 mg, 0.8 mmol). The mixture was stirred at room temperature for 2 hr. The product was obtained on removal of DMF and purified by silica gel column chromatography using ethyl acetate to provide compound **11b** ($R^1$=Me, $R^2$=Me $R^3$=H, $R^9$= 1-ethyl-propyl) (150 mg, 89%).

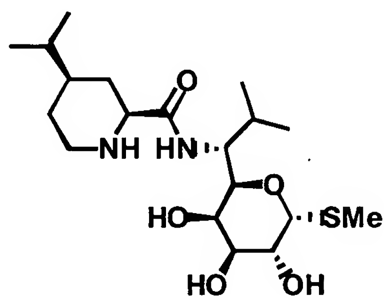
[0391] $^1$H NMR (300 MHz, $CD_3OD$) δ 8.42 (d, J=5.1, 1), 7.37 (s, 1), 7.32 (m, 1), 5.27 (d, J=4.8, 1), 4.21-4.88 (m, 3), 3.85 (d, J=3.6, 1), 3.56 (dd, J=3.3, 10.2, 1), 2.48 (m, 1), 2.11 (m, 4), 1.00 (m, 12). MS (ESPOS): 427 $[M+H]^+$.

[0392] To compound **11b** ($R^1$=Me, $R^2$=Me $R^3$=H, $R^9$= 1-ethyl-propyl) (130 mg, 0.3 mmol) in water (10 mL), AcOH (2 mL) and MeOH (2 mL), $PtO_2$ (150 mg) was added and hydrogenated at 55 psi overnight. The solvent was removed to obtain the crude product. Purification was carried by silica gel column chromatography using 20% MeOH in DCM to obtain the title compound (40 mg, 30%).

[0393] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, J=5.7, 1), 4.17 (dd, J=9.9; 3.3, 1), 4.10 (m, 2), 3.78 (m, 1), 3.51 (m, 2), 2.81 (m, 2), 2.16 (m, 1), 2.10 (s, 3) 1.90 (m, 2), 1.76 (m, 3), 1.40 (m, 8), 0.91 (m, 9); MS (ESPOS): 433 $[M+H]^+$.

## Example 28

**Preparation of 1-(4-iso-propylpiperid-6-yl)-N-{ 1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide**




[0394] 4-Isopropylpyridine-2-carboxylic acid, compound **(10b)** ($R^9$ = isopropyl), was made by employing Method P. To 4-isopropylpyridine (5 g, 0.041 mol) in acetic acid (60 mL), hydrogen peroxide (30%, 4.7 g, 0.13 mol) was added and refluxed over night. After removing the solvent, the residue was dissolved in DCM dried over magnesium sulfate and taken as such for the next step. To the resulting compound in dichloromethane (10 mL) trimethylsilyl cyanide (7.0 mL, 0.07 mol) and dimethylcarbamyl chloride (5.6 mL, 0.05 mol) were added and stirred at room temperature for 24 hours. Aqueous potassium carbonate (10%, 50 mL) was added and extracted with dichloromethane (100 mL). The crude product obtained on removal of solvent was taken up in hydrochloric acid (6N, 30 mL) and refluxed for 24 hours. Removal of acid

followed by crystallization of the crude product from acetonitrile resulted in acid **10b** ($R^9$ = isopropyl) (5g, 75%).

**[0395]** $^1$H NMR (300 MHz, $CD_3OD$): δ 8.78 (d, J = 6, 1), 8.42 (s, 1), 8.16 (d, J = 6.0, 1), 3.25 (m, 1), 1.33 (d, J = 9.0, 6) MS (ESNEG): 164 $[M-H]^-$.

**[0396]** To the amine, compound **2b** ($R^1$=Me, $R^2$=Me), (140 mg, 0.56 mmol) in DMF (3 mL), BSTFA (0.59 mL, 2.24 mmol) and triethylamine (0.18 mL, 1.26 mmol) were added at 0°C and the reaction mixture was stirred at room temperature for 3 hours. Acid **10b** ($R^9$ = isopropyl) (188 mg, 1.13 mmol) and HATU (319 mg, 0.84 mmol) were combined and left stirred for further 4 hours at room temperature. The DMF was removed and the residue was extracted with ethyl acetate (100 mL) and washed with saturated bicarbonate (40 mL). The product obtained on removal of solvent was taken up in methanol and treated with Dowex $H^+$ resin for 1 hour. After filtering the resin, methanol was removed to obtain the crude product. It was then purified on silica gel column using 10% methanol in dichloromethane as eluent to provide compound **11b** ($R^1$=Me, $R^2$=Me $R^3$=H, $R^9$ = isopropyl) (120 mg, 53 %).

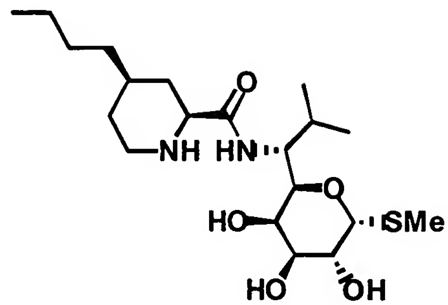
**[0397]** $^1$H NMR (300 MHz, $CD_3OD$): δ 8.42 (d, J=5.1, 1), 7.37 (s, 1), 7.32 (m, 1), 5.27 (d, J=4.8,1), 4.21-4.88 (m, 3), 3.85 (d, J=3.6, 1), 3.56 (dd, J=3.3, 10.2, 1), 2.48 (m, 1), 2.11 (m, 1), 2.10 (s, 3), 1.20 (m, 12). MS (ESPOS): 399 $[M+H]^+$.

**[0398]** To **11b** ($R^1$=Me, $R^2$=Me $R^3$=H, $R^9$ = isopropyl) (100 mg, 0. 257 mmol) in methanol (5 mL), water (10 mL) and acetic acid (5 mL), platinum dioxide (100 mg, 0.44 mmol) was added and hydrogenated at 60 psi for 16 h. After filtering the catalyst, the solvent was stripped off to obtain the crude product which was then purified on silica gel column chromatography using 10% methanol in dichloromethane as eluent. The lower $R_f$ compound was the title compound (10 mg, 9%).

**[0399]** $^1$H NMR (300 MHz, $CD_3OD$): δ 5.24 (d, J=5.7, 1), 4.17 (dd, J=9.9; 3.3, 1), 4.10 (m, 2), 3.80 (m, 1), 3.51 (m, 1), 3.16 (m, 1), 2.61 (m, 1), 2.16 (m, 1), 2.10 (s, 3) 1.90 (m, 1), 1.76 (m, 1), 1.50- 1.09 (m, 5), 0.91 (m, 12); MS (ESPOS): 405 $[M+H]^+$.

## Example 29

### Preparation of 1-(4-n-butylpiperid-6-yl)-N-{ 1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide



[0400] 4-Butylpyridine was prepared by adding potassium-t-butoxide (0.68 g, 6 mmol) to propylphosphonium bromide (Aldrich) (2.4 g, 6.0 mmol) in THF (10 mL), at 0 °C and stirring at room temperature for 1 hour. Pyridine-4-carbaldehyde (428 mg, 4 mmol) was added and the reaction mixture stirred for 2h. The reaction mixture was then poured into water and extracted with ethyl acetate. The product obtained after removing the solvent was taken as such in methanol (30 mL) to which palladium on carbon (10%, 300 mg) was added and hydrogenated at 1 atm pressure over night. Removal of solvent and purification on column chromatography using ethyl acetate resulted in pure product 4-butylpyridine (500 mg, 92%):

[0401] $^1$H NMR ($CDCl_3$): δ 8.42 (d, J = 6.0, 2), 7.05 (d, J = 6.0, 1), 2.60 (t, J = 6.5, 2), 1.62 (m, 2), 1.37 (m, 2), 0.93 (t, J = 7.0, 3). MS (ESPOS): 136 $[M+H]^+$.

[0402] 4-Butylpyridine-2-carboxylic acid, compound **(10b)** ($R^9$ = butyl), was made employing Method P. To 4-butylpyridine (2 g, 0.014 mol) in acetic acid (15 mL), hydrogen peroxide (30%, 5 mL, 0.056 mol) was added and refluxed over night. After removing the solvent, the residue was dissolved in DCM dried over magnesium sulfate and taken as such for the next step. To the compound from the previous step in dichloromethane (10 mL) trimethylsilyl cyanide (3.92 mL, 0.029 mol) and dimethylcarbamoyl chloride (2.67 mL, 0.028 mol) was added and stirred at room temperature for 24 hours. Aqueous potassium carbonate (10%, 50 mL) was added and extracted with dichloromethane (100 mL). The crude product obtained on removal of solvent was taken up in hydrochloric acid (6N, 30 mL) and refluxed for 24 hours. Removal of acid followed by crystallization of the crude product from acetonitrile resulted in acid **10b** ($R^9$ = butyl) (1.5g, 60%).

[0403] $^1$H NMR ($CDCl_3$): δ 8.92 (d, J = 6.0, 1), 8.65 (s, 1), 8.27 (m, 1), 3.23 (t, J = 6.5, 2), 1.98 (m, 2), 1.67 (m, 2), 1.20 (t, J = 7.0, 3). MS (ESNEG): 178 $[M-H]^-$.

[0404] To the amine, compound **2b** ($R^1$=Me, $R^2$=Me), (140 mg, 0.56 mmol) in DMF (3 mL), BSTFA (0.59 mL, 2.24 mmol) and triethylamine (0.18 mL, 1.26 mmol) were added at 0 °C and then stirred at room temperature for 3 hours. Acid **10b** ($R^9$ = butyl) (203 mg, 1.13 mmol) and

HATU (319 mg, 0.84 mmol) were added and the reaction mixture was stirred for 4 more hours at room temperature. The DMF was removed and the residue was extracted with ethyl acetate (100 mL) and washed with saturated bicarbonate (40 mL). The product obtained on removal of solvent was taken up in methanol and treated with Dowex $H^+$ resin for 1 hour. After filtering the resin, methanol was removed to obtain the crude product. The product was then purified on silica gel column using ethyl acetate as eluent to provide for compound **11b** ($R^1$=Me, $R^2$=Me $R^3$=H, $R^9$ = butyl) (200 mg, 86 %).

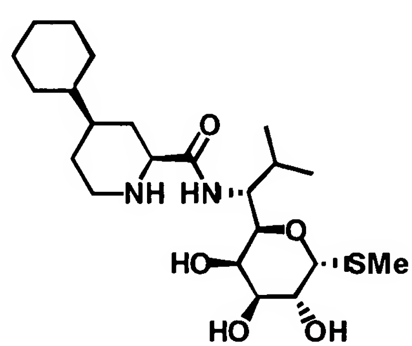
**[0405]** $^1$H NMR ($CDCl_3$) δ 8.40 (d, J = 4.2, 1), 8.01 (s, 1), 7.29 (m, 1), 5.40 (d, J = 5.4, 1), 4.02-4.36 (m, 3), 4.80 (s, 1), 3.48-3.60 (m, 1), 3.72 (t, J = 6.0, 2), 2.49 (m, 1), 2.20 9s, 3), 1.67 (m, 4), 1.40 (m, 3), 0.98-1.18 (m, 9). Mass 413 $[M+H]^+$.

**[0406]** To compound 11b ($R^1$=Me, $R^2$=Me $R^3$=H, $R^9$ = butyl) (200 mg, 0. 49 mmol) in methanol (5 mL), water (10 mL) and acetic acid (5 mL), platinum dioxide (100 mg, 0.44 mmol) was added and hydrogenated at 60 psi for 16 h. After filtering the catalyst, the solvent was stripped off to obtain the crude product, which was then purified on silica gel column chromatography using 20% methanol in dichloromethane as eluent. The lower $R_f$ fractions provided the title compound (60 mg, 29%).

**[0407]** $^1$H NMR ($CDCl_3$): δ 5.20 (d, J = 3.6, 1), 4.20 (dd, J = 3.0, 4.8, 1), 4.04 (m, 2), 3.80 (d, J =3.0, 1), 3.61-3.66 (m, 1), 3.52 (dd, J = 3.3, 10.2), 2.88 (m, 1), 2.17 (m, 1), 2.14 (s, 3), 1.87 (m, 2), 1.62 (m, 2), 1.32 (m, 6), 0.89 (m, 9); MS (ESPOS): 419 $[M+H]^+$.

## Example 30

### Preparation of 1-(4-cyclohexylpiperid-6-yl)-N-{ 1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide



[0408] 4-phenylpyridine-2-carboxylic acid, compound **10b** ($R^9$ =phenyl), was made by employing Method P. To 4-phenylpyridine-N-oxide (1 g, 5.84 mmol) in dichloromethane (10 mL) trimethylsilyl cyanide (1.5 mL, 11.6 mmol) and dimethylcarbamoyl chloride (1 mL, 11.6 mmol) were added and the reaction mixture was stirred at room temperature for 24 hours. An aqueous potassium carbonate solution (10%, 10 mL) was added and extracted with dichloromethane (100 mL). The crude product obtained on removal of solvent was taken up in hydrochloric acid (6N, 30 mL) and refluxed for 24 hours. Removal of acid followed by crystallization of the crude product from acetonitrile resulted in acid **10b** ($R^{9'}$ = phenyl) (1 g, 86%).

[0409] MS (ESNEG): 198 $[M-H]^-$; $^1H$ NMR (300 MHz, $CD_3OD$) δ 7.64-7.67 (m, 3), 8.02-8.06 (m, 2), 8.53-8.56 (m, 1), 8.82 (s, 1), 8.82-8.90 (m, 1).

[0410] To the amine **2b** ($R^1$=Me, $R^2$=Me) (102 mg, 0.42 mmol) in DMF (5 mL), BSTFA (0.549 mL, 2.1 mmol) and triethylamine (0.183 mL, 1.26 mmol) was added at 0 °C and then stirred at room temperature for 3 hours. Acid **10b** ($R^9$=phenyl) (158 mg, 0.80 mmol) and HATU (302 mg, 0.80 mmol) were added and the reaction was stirred for an additional 4 hours at room temperature. The DMF was removed and the residue was extracted with ethyl acetate (100 mL) and washed with saturated bicarbonate (40 mL). The product obtained on removal of solvent was taken up in methanol and treated with Dowex $H^+$ resin for 1 hour. After filtering the resin, methanol was removed to obtain the crude product. The resulting residue was then purified by silica gel chromatography using 10% methanol in dichloromethane as eluent to provide compound **11b**($R^1$=Me, $R^2$=Me $R^3$=H, $R^{9'}$ = phenyl) (50 mg, 58 %).

[0411] TLC: Rf = 0.70 (10% MeOH/DCM); MS (ESPOS): 435 $[M+H]^+$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.01 (t, J = 6.6, 6), 2.12 (s, 3), 2.28 (m, 1), 3.56 (dd, J = 3.3, 10.5, 1), 3.90 (d, J = 3.3, 1), 4.12 (dd, J = 5.4, 10.5, 1), 4.27-4.36 (m, 2), 4.52 (m, 2), 5.26 (d, J = 5.7, 1), 7.48-7.55 (m, 3), 7.77-7.80 (m, 2), 7.83-7.85 (m, 1), 8.37 (s, 1), 8.69 (d, J = 5.4, 1).

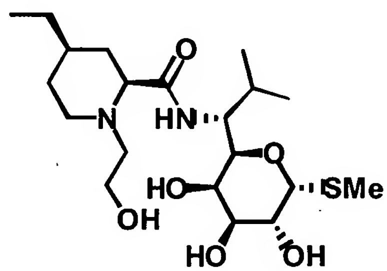
[0412] To compound 11b ($R^1$=Me, $R^2$=Me $R^3$=H, $R^{9'}$ = phenyl) (40 mg, 0.09 mmol) in methanol (5 mL), water (10 mL) and acetic acid (5 mL), platinum dioxide (100 mg, 0.44 mmol) was added and the reaction mixture shaken at 60 psi hydrogen for 16 h. The catalyst was removed by filtration, and the solvent was evaporated to obtain the crude product, which was then purified on silica gel column chromatography using 10% methanol in dichloromethane to provide the title compound (10 mg, 25%).

[0413] TLC: $R_f$= 0.22 (20% MeOH/DCM); MS (ESPOS): 447 $[M+H]^+$; $^1H$ NMR (300 MHz, $CD_3OD$) δ 0.90 (d, J = 6.8, 6), 0.93-1.05 (m, 5), 1.20 (m, 6), 1.33-1.47 (m, 4), 1.75 (m, 6),

2.10 (s, 3), 2.18-2.22 (m, 1), 2.97 (t, J = 12.3, 1), 3.39-3.52 (m, 2), 3.70-3.78 (m, 2), 4.05-4.21 (m, 3), 5.23 (d, J = 5.7, 1).

### Example 31

### Preparation of 1-( 4-ethyl-N-hydroxyethyl-piperid-6-yl)-N-{ 1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide

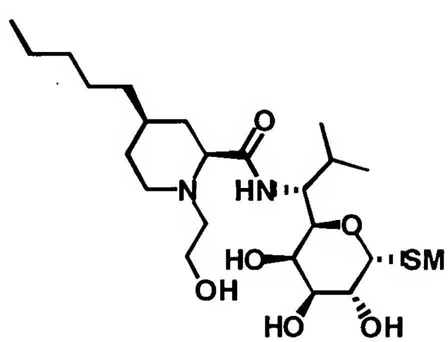


[0414] To the product of Example 1 (28 mg, 0.07 mmol) in methanol (2 mL), ethylene oxide (0.5 mL) was added and stirred at 4 °C overnight. The solvent was removed and the resulting product was purified by column chromatography using 20% MeOH in DCM as eluent to obtain the title compound (16 mg, 51%) as a white powder.

[0415] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, J = 6, 1), 4.27 (m, 1), 4.10 (m, 2), 3.95 (m, 1), 3.79-3.50 (m, 4), 3.85 (m, 1) 3.74 (m, 1), 3.26 (m, 1), 2.91 (m, 2), 2.33 (m, 1), 2.13 (m, 4), 1.92 (m, 1), 1.71 (m, 1), 1.17 (m, 7), 0.94 (m, 9); MS (ESPOS): 435 $[M+H]^+$.

### Example 32

### Preparation of 1-( 4-n-pentyl-N-hydroxyethyl-piperid-6-yl)-N-{ 1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide

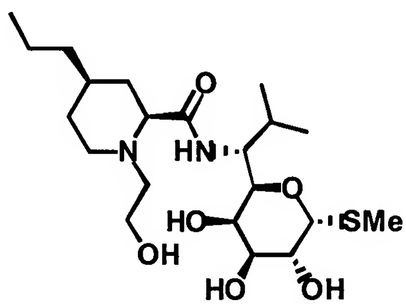


[0416] The title compound was prepared using the procedures of Example **32** with the product from Example **25** as the starting material.

[0417] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, J=6.0, 1), 4.19 (m, 3), 3.79 (d, J=3.3, 1), 3.74 (m, 1), 3.65 (m, 1), 3.54 (dd, J=3.0, 10.2, 1), 3.25 (m, 2), 2.82 (m, 2), 2.14 (m, 4), 1.89 (m, 1), 1.72 (m, 1), 1.28 (m, 12), 0.94 (m, 9); MS (ESPOS): 477 $[M+H]^+$.

## Example 33

### Preparation of 1-( 4-n-propyl-N-hydroxyethyl-piperid-6-yl)-N-{ 1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide

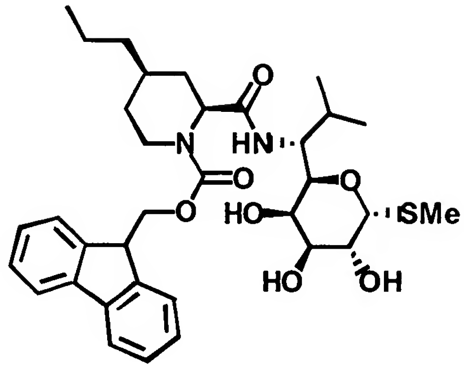



[0418] The title compound was made using the procedures of Example **32** with the product of Example **17** as the starting material.

[0419] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, J=6.0, 1), 4.19 (dd, J=9.6; 3.3, 1), 4.11 (m, 2), 3.79 (d, J=3.3, 1), 3.75 (m, 1), 3.65 (m, 1), 3.54 (m, 1), 3.28 (m, 1), 2.82 (m, 2), 2.27 (m, 5) 1.90 (m, 1), 1.71 (m, 1), 1.36 (m, 8), 0.94 (m, 9); MS (ESPOS): 449 $[M+H]^+$.

## Example 34

### Preparation of 1-[4-n-propyl-N-(F-moc)-piperid-6-yl]-N-{ 1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide

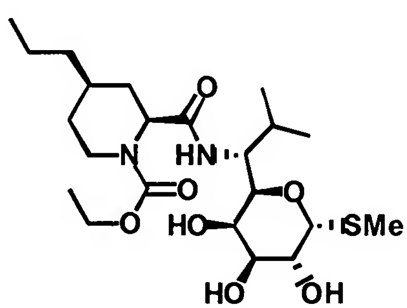


[0420] To the product of Example **17** (50 mg, 0.123 mmol) in water (3 mL) and dioxane (3 mL), Fmoc-Cl (38mg, 0.197 mmol) and sodium carbonate (25 mg, 0.246 mmol) were added and the reaction mixture was stirred over night at room temperature. The solvents were removed and the crude material was loaded into a silica gel column and eluted with ethyl acetate to obtain the title compound as a white solid (30 mg, 51%).

[0421] TLC: Rf = 0.5 (EtOAc). MS (ESPOS): 627 $[M+H]^+$, 649 $[M+Na]^+$; $^1H$ NMR ($CD_3OD$, 200 MHz): 7.79 (d, J = 4.6 Hz, 2), 7.59-7.62 (m, 2), 7.28-7.41 (m, 4), 5.19 (d, J = 3.8 Hz, 1), 4.45 (m, 2), 4.24 (t, J = 4.2, 1), 3.99-4.15 (m, 4), 3.93 (m, 1), 3.47-3.50 (m, 2), 2.05 (s, 3), 1.87 (m, 1), 1.67 (s, 2), 1.50 (m, 1), 1.30 (m, 4), 0.86-0.91 (m, 9).

### Example 35

### Preparation of 1-[4-n-propyl-N-(carboxylic acid ethyl ester)-piperid-6-yl]-N-{ 1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide

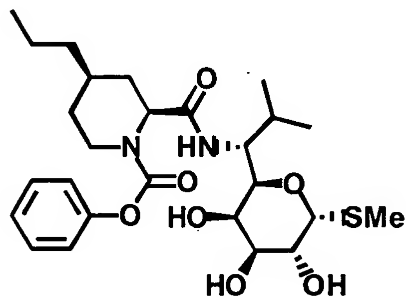


[0422] To the product of Example **17** (50 mg, 0.123 mmol) in water (3 mL) and dioxane (3 mL), ethyl chloroformate (20 mg, 0.147 mmol) and sodium carbonate (25 mg, 0.246 mmol) were added and stirred over night at room temperature. The solvents were removed and the crude material was loaded into a silica gel column and eluted with ethyl acetate to obtain the title compound as a white solid (40 mg, 52%).

[0423] TLC: Rf = 0.28 (EtOAc). MS (ESPOS): 477 $[M+H]^+$; 499 $[M+Na]^+$; $^1H$ NMR ($CD_3OD$, 200 MHz): 5.22 (d, J = 3.6 Hz, 1), 4.27 (m, 1), 4.03-4.14 (m, 5), 3.96 (bs, 1), 3.62 (m, 1), 3.54 (d, J = 2.2 Hz, 1), 3.52 (d, J = 2.2 Hz, 1), 2.08 (s, 3), 1.93-2.03 (m, 2), 1.75-1.85 (m, 3), 1.61 (m, 2), 1.33 (m, 4), 1.22-1.28 (m, 3), 0.90-0.94 (m, 9).

## Example 36

### Preparation of 1-[4-n-propyl-N-(carboxylic acid phenyl ester)-piperid-6-yl]-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide

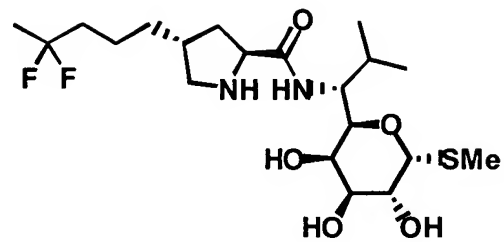


[0424] To the product of Example **17** (50 mg, 0.123 mmol) in water (3 mL) and dioxane (3 mL), phenyl chloroformate (40 mg, 0.246 mmol) and sodium carbonate (25 mg, 0.246 mmol) were added and the reaction mixture was stirred over night at room temperature. The solvents were removed and the crude material was loaded into a silica gel column and eluted with ethyl acetate to obtain the title compound as a white solid (30 mg, 47%).

[0425] TLC: Rf = 0.4 (EtOAc). MS (ESPOS): 526 $[M+H]^+$, 548 $[M+Na]^+$; $^1H$ NMR ($CD_3OD$, 200 MHz): 7.36 (t, J = 3.8 Hz, 2), 7.17-7.23 (m, 10), 7.10 (d, J = 3.6 Hz, 2), 5.20 (d, J = 3.6 Hz, 1), 4.09 (m, 3), 3.93 (d, J = 2.2 Hz, 1), 3.82 (m, 2), 3.46 (m, 2), 2.01 (s, 3), 2.00 (m, 1), 1.71 (m, 1), 1.46-1.36 (m, 4), 0.96-0.90 (m, 9).

## Example 37

### Preparation of 1-[4- (4,4-difluoropent-1-yl) pyrrolidin-2-yl]-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide



[0426] To a solution of aldehyde **8a,** prepared by first step in Method L, (510 mg, 1.47 mmol, 1 equiv) in benzene (8 mL) was added 1-triphenylphosphoranylidene-2-propanone (Aldrich) (702 mg, 2.2 mmol, 1.5 equiv). The reaction mixture was refluxed overnight and the solvent was removed under vacuum. The residue was purified by chromatography to give 4-(4-oxo-pent-2-enyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester as an oil (237 mg, 42 %).

[0427] MS (ESPOS): 410.2 $[M + Na]^+$, 288.3 $[M - Boc + H]^+$; MS (ESNEG): 386.2 $[M-H]^-$.

[0428] To a solution of 4-(4-oxo-pent-2-enyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (193 mg, 0.5 mmol, 1 equiv) in benzene (0.9 mL) was added a solution of triphenylphosphine-copper (I) hydride hexamer in benzene (3.6 mL). The mixture was stirred at rt overnight and hexane (13 mL) was added. The mixture was filtered and the filtrate was evaporated. The residue was purified by chromatography to give 4-(4-oxo-pentyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (127 mg, 65 %).

[0429] $^1$H NMR (300 MHz, $CDCl_3$) δ 7.35-7.30 (m, 5), 5.25-5.04 (m, 2), 4.42-4.25 (m, 1), 3.77-3.62 (m, 1), 3.00-2.85 (m, 1), 2.39 (t, J = 7, 2), 2.34-1.47 (m, 7), 2.10 (s, 3), 1.43 (s, 3H), 1.31 (s, 6H); MS (ESPOS): 412.3 $[M + Na]^+$, 290.3 $[M - Boc + H]^+$; MS (ESNEG): 388.4 $[M-H]^-$.

[0430] To a solution of 4-(4-oxo-pentyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (155 mg, 0.40 mmol, 1 equiv) in dichloromethane (1.5 mL) at –78 °C was added DAST (0.21 mL, 1.60 mmol, 4 equiv). The reaction mixture was warmed to rt and stirred at rt for 3 h, followed by additional DAST (0.32 mL, 2.4 mmol, 6 equiv) at -78 °C. The mixture was warmed to rt and stirred overnight. Then the mixture was diluted with dichloromethane, washed with sat. aqueous $NaHCO_3$ (1x), dried, and evaporated. The residue was purified by chromatography to give 4-(4,4-difluoro-pentyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester as a yellow oil (88 mg, 54 %).

[0431] MS (ESPOS): 434.2 $[M + Na]^+$, 312.3 $[M - Boc + H]^+$.

[0432] To a solution of 4-(4,4-difluoro-pentyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (88 mg, 0.21 mmol, 1 equiv) in THF (1.2 mL) and water (0.4 mL) was added lithium hydroxide monohydrate (45 mg, 1.07 mmol, 5 equiv). The reaction mixture was stirred at rt overnight. The THF was removed under vacuum. The residue was diluted with water and washed with ether. The aqueous layer was taken up in ethyl acetate, partitioned with 10% citric acid. The organic layer was washed with water (1 x), brine (1 x), dried and concentrated to give 4-(4,4-difluoro-pentyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (66 mg, 96 %).

[0433] $^1$H NMR (300 MHz, $CDCl_3$) δ 4.39-4.34 (m, 1), 3.57-3.48 (m, 1), 2.92-2.83 (m, 1), 2.57-2.50 (m, 1), 2.30-2.18 (m,1), 1.91-1.73 (m, 3), 1.64-1.36 (m, 7), 1.48 (s, 9); MS (ESPOS): 344.3 $[M + Na]^+$, 222.3 $[M - Boc + H]^+$; MS (ESNEG): 320.2 $[M-H]^-$.

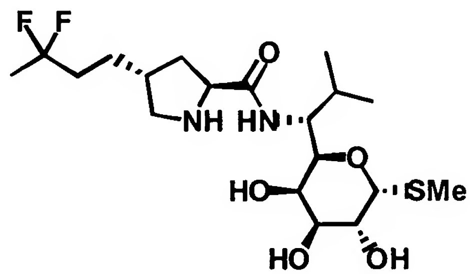
[0434] To a solution of compound **2b** ($R^1$=Me, $R^2$=Me) (50 mg, 0.20 mmol, 1 equiv) in dry DMF (0.5 mL) at 0 °C was added triethylamine (88.3 up, 0.64 mmol, 3.2 equiv), followed by the addition of BSTFA (79.2 $\mu$L, 0.30 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C for 10 minutes, and then was stirred at rt for 50 minutes. The reaction mixture was added to the acid (66 mg, 0.21 mmol, 1 equiv) in a 25 mL round bottom flask, followed by the addition of HATU (96.8 mg, 0.25 mmol, 1.25 equiv). The reaction mixture was stirred at rt for 3 h. The reaction mixture was evaporated to dryness, taken up in ethyl acetate, washed with 10% citric acid, water, sat. $NaHCO_3$ and brine. The organic layer was dried over $Na_2SO_4$ and evaporated and used in the next step without additional purification.

[0435] To a solution of the above Boc protected lincosamide in DCM (9 mL) with methyl sulfide (0.20 mL) were added trifluoroacetic acid (3 mL) and water (0.20 mL). The reaction mixture was stirred at rt for 1 h. The solvent was removed under vacuum and co-evaporated with toluene twice. The residue was purified by chromatography to provide the title compound (68 mg, 75 %) as a white solid.

[0436] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, J = 5.4, 1), 4.16 (dd, J = 3.3, 9.9, 1), 4.11-4.00 (m, 3), 3.75 (d, J = 3.3, 1), 3.51 (dd, J = 3.3, 10.2, 1), 3.40-3.32 (m, 1), 2.71 (dd, J = 8.2, 10.6, 1), 2.23-2.05 (m, 3), 2.10 (s, 3), 1.98-1.76 (m, 3), 1.63-1.39 (m, 7), 0.94-0.87 (m, 6). MS (ESPOS): 455.3 $[M+H]^+$.

## Example 38

### Preparation of 1-[4-(3,3-difluorobut-1-yl)pyrrolidin-2-yl]-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide



[0437] Ethyl triphenylphosphonium bromide (Aldrich) (2.92 g, 7.86 mmol, 3.9 equiv) and potassium-t-butoxide (0.61 g, 5.44 mmol, 2.7 equiv) were suspended in toluene (26 mL) under nitrogen with vigorous stirring. After 4 h, a solution of aldehyde **8a** prepared by the first step in Method L (700 mg, 2.01 mmol, 1 equiv) in toluene (17 mL) was added dropwise. The reaction mixture was stirred at rt for 2 h and diluted with ethyl acetate (150 mL). The organic layer was washed with water (2x), brine, dried and concentrated. The residue was purified by chromatography to give a clear oil 4-but-2-enyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (360 mg, 50 %).

[0438] MS (ESPOS): 260.3 $[M+H - Boc]^+$.

[0439] To a solution of 4-but-2-enyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (149 mg, 0.42 mmol, 1 equiv) in DMF (1.4 mL) and water (0.2 mL) were added palladium(II)chloride (7.4 mg, 0.042 mmol, 0.1 equiv) and copper(I) chloride (41.1 mg, 0.42 mmol, 1 equiv). The mixture was stirred at 50 °C overnight with oxygen bubbling into the mixture. The mixture was filtered and the filtrate was concentrated under high vacuum. The residue was diluted with ethyl acetate, washed with water (1x), brine (1x), dried and concentrated. The residue was purified by preparative TLC to give 4-(3-oxo-butyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (110 mg, 71 %).

[0440] $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.35-7.28 (m, 5), 5.24-5.03 (m, 2), 4.43-4.25 (m, 1), 3.75-3.61 (m, 1), 3.01-2.87 (m, 1), 2.44-2.35 (m,2), 2.28-2.15 (m, 1), 2.11 (s, 3), 2.09-1.98 (m, 1), 1.91-1.51 (m, 3), 1.43 (s, 3.4H), 1.31 (s, 5.6H). MS (ESPOS): 398.3 $[M + Na]^+$, 276.3 $[M - Boc + H]^+$.

[0441] To a solution of the 4-(3-oxo-butyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (110 mg, 0.29 mmol, 1 equiv) in dichloromethane (1.1 mL) at –78 °C was added DAST (0.16 mL, 1.17 mmol, 4 equiv). The reaction mixture was warmed to rt and stirred at rt for 3 h, followed by additional DAST (0.23 mL, 1.76 mmol, 6 equiv) at -78 °C. The mixture was warmed to rt and stirred overnight. Then the mixture was diluted with dichloromethane, washed with sat. aqueous $NaHCO_3$ (1x), dried, evaporated. The residue was purified by chromatography to give 4-(3,3-Difluoro-butyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (92.7 mg, 80 %).

[0442] MS (ESPOS): 420.3 $[M + Na]^+$.

[0443] To a mixture of 4-(3,3-difluoro-butyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (92.7 mg, 0.23 mmol, 1 equiv) in THF (1.2 mL) and water (0.4 mL) was added lithium hydroxide monohydrate (49 mg, 1.17 mmol, 5 equiv). The reaction mixture was stirred at rt overnight. the THF was removed under vacuum. The residue was diluted with water, washed with ether. The aqueous layer was taken up in ethyl acetate, partitioned with 10% citric acid. The organic layer was washed with water (1 x), brine (1 x), dried and concentrated to give a white solid, 4-(3,3-difluoro-butyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (59.7 mg, 83 %).

[0444] $^1$H NMR (300 MHz, $CDCl_3$) δ 4.40-4.36 (m, 1), 3.59-3.52 (m, 1), 2.94-2.86 (m, 1), 2.55-2.48 (m, 1), 2.33-2.15 (m, 1), 1.92-1.73 (m, 3), 1.66-1.40 (m, 5), 1.47 (s, 9); MS (ESPOS): 330.2 $[M + Na]^+$, 208.2 $[M - Boc + H]^+$; MS (ESNEG): 306.1 $[M-H]^-$.

[0445] To a solution of compound **2b** ($R^1$=Me, $R^2$=Me) (50 mg, 0.20 mmol, 1 equiv) in dry DMF (0.5 mL) at 0 °C was added triethylamine (88.3 up, 0.64 mmol, 3.2 equiv), followed by the addition of BSTFA (79.2 μL, 0.30 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C for 10 minutes, and then was stirred at rt for 50 minutes. The reaction mixture was added to the acid 4-(3,3-difluoro-butyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (59.7 mg, 0.20 mmol, 1 equiv) in a 25 mL round bottom flask, followed by the addition of HATU (93.3 mg, 0.25 mmol, 1.25 equiv). The reaction mixture was stirred at rt for 3 h. The reaction mixture was evaporated to dryness, taken up in ethyl acetate, washed with 10% citric acid, water, sat. $NaHCO_3$ and brine. The organic layer was dried over $Na_2SO_4$ and evaporated to give a syrup.

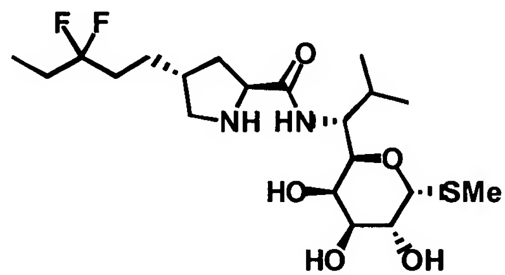
[0446] To a solution of the above syrup in DCM (9 mL) with methyl sulfide (0.20 mL) were added trifluoroacetic acid (3 mL) and water (0.20 mL). The reaction mixture was stirred at rt for 1 h. The solvent was removed under vacuum and co-evaporated with toluene twice. The

residue was purified by chromatography to provide the title compound (63 mg, 72 %) as a white solid.

[0447] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, J = 5.7, 1), 4.22-4.13 (m, 2), 4.10-4.04 (m, 2), 3.76 (d, J = 2.4, 1), 3.54-3.42 (m, 2), 2.84-2.76 (m, 1), 2.29-1.83 (m, 5), 2.10 (s, 3), 1.67-1.51 (m, 6), 0.95-0.87 (m, 6). MS (ESPOS): 441.3 $[M+H]^+$

## Example 39

### Preparation of 1-[4-(3,3-difluoropent-1-yl)pyrrolidin-2-yl]-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide



[0448] To a solution of compound **7c** ($R^{9'}$=2-penteneyl) prepared using methods of Method K (323.7 mg, 0.87 mmol, 1 equiv) in DMF (2.8 mL) and water (0.4 mL) at 0 °C were added palladium (II) chloride (15.4 mg, 0.087 mmol, 0.1 equiv) and copper(I) chloride (85.9 mg, 0.87 mmol, 1 equiv). The mixture was stirred at 50 °C overnight with oxygen bubbling into the mixture. The mixture was filtered and the filtrate was concentrated under high vacuum. The residue was diluted with ethyl acetate, washed with water (1x), brine (1x), dried and concentrated. The residue was purified by preparative TLC to provide 4-(3-oxo-pentyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (242 mg, 72 %).

[0449] MS (ESPOS): 412.3 $[M + Na]^+$, 290.3 $[M - Boc + H]^+$.

[0450] To 4-(3-oxo-pentyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (242 mg, 0.62 mmol, 1 equiv) in dichloromethane (2.3 mL) at –78 °C was added DAST (0.33 mL, 2.49 mmol, 4 equiv). The reaction mixture was warmed to rt and stirred at rt for 3 h, followed by an addition of more DAST (0.49 mL, 3.73 mmol, 6 equiv) at –78 °C. The mixture was warmed to rt and stirred overnight. Then the mixture was diluted with dichloromethane, washed with sat. aqueous $NaHCO_3$ (1x), dried, evaporated. The residue was purified by

chromatography to 4-(3,3-Difluoro-pentyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (117 mg, 46%).

**[0451]** $^1$H NMR (300 MHz, $CDCl_3$ ) δ 7.35-7.26 (m, 5), 5.25-5.04 (m, 2), 4.44-4.27 (m, 1), 3.79-3.64 (m, 1), 3.02-2.89 (m, 1), 2.32-2.17 (m,1), 2.13-2.02 (m, 1), 1.91-1.68 (m, 5), 1.57-1.47 (m, 2), 1.44 (s, 3.5H), 1.31 (s, 5.5H), 0.97 (t, J = 7.5, 3).

MS (ESPOS): 434.3 $[M + Na]^+$, 312.3 $[M - Boc + H]^+$.

**[0452]** To a solution of 4-(3,3-difluoro-pentyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (106 mg, 0.26 mmol, 1 equiv) in THF (2.4 mL) and water (0.8 mL) was added lithium hydroxide monohydrate (54 mg, 1.29 mmol, 5 equiv). The reaction mixture was stirred at rt overnight. THF was removed under vacuum. The residue was diluted with water (10 mL), washed with ether (20 mL). The aqueous layer was taken up in ethyl acetate (50 mL), partitioned with 10% citric acid (25 mL). The organic layer was washed with water (1 x), brine (1 x), dried and concentrated to give 4-(3,3-difluoro-pentyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester as a clear oil (82.1 mg, 99%).

**[0453]** $^1$H NMR (300 MHz, $CDCl_3$) δ 4.40-4.36 (m, 1), 3.58-3.51 (m, 1), 2.94-2.86 (m, 1), 2.57-2.51 (m, 1), 2.30-2.15 (m,1), 1.92-1.72 (m, 5), 1.62-1.53 (m, 2), 1.48 (s, 9), 0.99 (t, J = 7.5, 3); MS (ESPOS): 344.3 $[M + Na]^+$, 222.3 $[M - Boc + H]^+$.

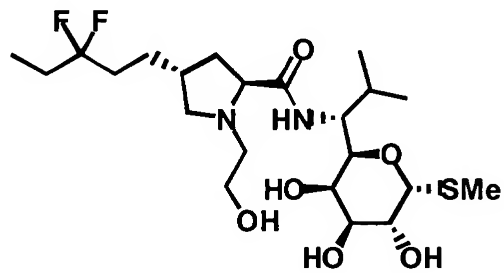
**[0454]** To a solution of compound **2b** ($R^1$=Me, $R^2$=Me) (50 mg, 0.20 mmol, 1 equiv) in dry DMF (0.5 mL) at 0 °C was added triethylamine (88.3 μL, 0.64 mmol, 3.2 equiv), followed by the addition of BSTFA (79.2 μL, 0.30 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C for 10 minutes, and then was stirred at rt for 50 minutes. The reaction mixture was added to the acid 4-(3,3-difluoro-pentyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (76.6 mg, 0.24 mmol, 1.2 equiv) in a 25 mL round bottom flask, followed by the addition of HATU (111.9 mg, 0.29 mmol, 1.5 equiv). The reaction mixture was stirred at rt for 3 h. The reaction mixture was evaporated to dryness, taken up in ethyl acetate (60 mL), washed with 10% citric acid (30 mL), water (30 mL), sat. $NaHCO_3$ (30 mL) and brine. The organic layer was dried over $Na_2SO_4$ and evaporated to give a yellow oil.

**[0455]** To a solution of the above oil in DCM (9 mL) with methyl sulfide (0.20 mL) were added trifluoroacetic acid (3 mL) and water (0.20 mL). The reaction mixture was stirred at rt for 1 h. The solvent was removed under vacuum and co-evaporated with toluene twice. The residue was purified by chromatography to provide the title compound (72 mg, 80%) as a white solid.

[0456] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, J = 5.7, 1), 4.20-4.04 (m, 4), 3.76 (d, J = 2.7, 1), 3.51 (dd, J = 3.4, 10.3, 1), 3.43 (dd, J = 6.9, 10.8, 1), 2.77 (dd, J = 8.4, 10.8, 1), 2.30-2.05 (m, 3), 2.10 (s, 3), 2.03-1.76 (m, 5), 1.64-1.54 (m, 2), 1.03-0.89 (m, 9); MS (ESPOS): 455.4 $[M+H]^+$.

## Example 40

**Preparation of 1-[4-(3,3-difluoropent-1-yl)-N-(2-hydroxyeth-1-yl)pyrrolidin-2-yl]-N-{1-[3,4,5-trihydroxy-6- (methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide**

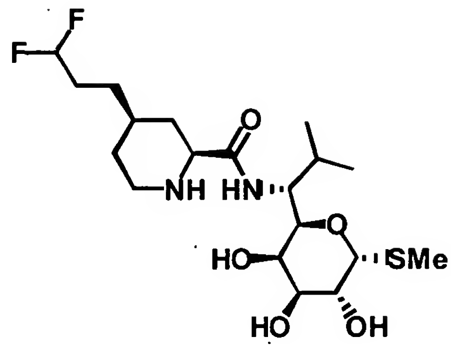


[0457] To a solution of the product of Example **42** (17.9 mg, 0.039 mmol) in MeOH (2 mL) at 0 °C was added ethylene oxide (0.4 mL). The reaction mixture was stirred at 4 °C overnight. The reaction mixture was concentrated and purified by chromatography to give the title compound as a white solid (8.2 mg, 42%).

[0458] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.23 (d, J = 5.7, 1), 4.13-4.05 (m, 3), 3.75 (d, J = 3.6, 1), 3.72-3.57 (m, 2), 3.53 (dd, J = 3.3, 10.2, 1), 3.41-3.36 (m, 1), 3.22 (dd, J = 3.3, 10.8, 1), 2.88-2.78 (m, 1), 2.63-2.54 (m, 1), 2.18-1.99 (m, 4), 2.10 (s, 3), 1.93-1.75 (m, 5), 1.57-1.46 (m, 2), 1.01-0.90 (m, 9); MS (ESPOS): 499.6 $[M+H]^+$; MS (ESNEG): 497.5 $[M-H]^-$.

## Example 41

**Preparation of 1-(4-(3,3-difluoroprop-1-yl)piperid-6-yl)-N-{ 1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide**



[0459] Compound **14c** ($R^9$ = 2,2-difluoroethyl) is prepared using the methods described in Method R.

[0460] To a dry flask were added compound **14a** (1.4 g, 5.32 mmol, 1 equiv), , triphenylphosphine (111.6 mg, 0.43 mmol, 0.08 equiv), copper (I) iodide (81 mg, 0.43 mmol, 0.08 equiv), palladium acetate (47.7 mg, 0.21 mmol, 0.04 equiv) and triethylamine (20 mL). The mixture was deaerated with nitrogen, followed by addition of propiolaldehyde diethyl acetyl (1.36 g, 10.65 mmol, 2 equiv). The mixture was stirred at rt for 3 hrs. The solvent was removed under vacuum to give a dark residue. The residue was purified by chromatography to give a yellow oil, compound **14b** ($R^{9'}$= 3,3-Diethoxy-prop-1-ynyl) (1.4 g, 100%).

[0461] $^1$H NMR (300 MHz, $CDCl_3$) δ 8.69 (dd, J = 0.8, 5.0, 1), 8.15 (dd, J = 0.8, 1.4, 1), 7.49 (dd, J = 1.7, 5.0, 1), 5.48 (s, 1), 3.99 (s, 3), 3.82-3.73 (m, 2), 3.71-3.62(m, 2), 1.26 (t, J = 7.2, 6). MS (ESPOS): 264.5 $[M+H]^+$.

[0462] To a solution of **14b** ($R^{9'}$= 3,3-Diethoxy-prop-1-ynyl) (1.4 g, 5.32 mmol) in methanol (100 mL) was added 10 % palladium on carbon (0.3 g). The mixture was purged and charged with hydrogen (1 atm) and shaken at rt overnight. The palladium was removed by filtration and the filtrate was concentrated to give **14c** ($R^9$=3,3-diethoxy propyl) as an oil (1.39 g, 98%).

[0463] $^1$H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, J = 5.1, 1), 7.98 (d, J = 0.9, 1), 7.31-7.28 (m, 1), 4.45 (t, J = 5.4, 1), 3.98 (s, 3), 3.72-3.58 (m, 2), 3.52-3.39(m, 2), 2.79-2.72 (m, 2), 1.99-1.90 (m, 2), 1.22-1.15 (m, 6).

[0464] To a mixture of **14c** ($R^9$=3,3-diethoxy propyl) (0.68 g, 2.55 mmol) in acetic acid (8 mL) and water (2 mL) was added conc. hydrochloric acid (2 drops). The mixture was stirred at rt overnight and the solvent was removed under high vacuum. The residue was diluted with ethyl acetate, washed with sat. sodium bicarbonate (1x), brine (1x). The organic layer was dried and concentrated to give 4-(3-Oxo-propyl)-pyridine-2-carboxylic acid methyl ester as a yellow oil (0.27 g, 55 %).

[0465] To a solution of aldehyde 4-(3-oxo-propyl)-pyridine-2-carboxylic acid methyl ester (0.27 g, 1.4 mmol, 1 equiv) in DCM (5 mL) at -78 °C was added DAST (0.91 g, 5.6 mmol, 4 equiv). The mixture was warmed to rt and stirred overnight. The mixture was diluted with dichloromethane (60 mL), washed with sat. aqueous $NaHCO_3$ (1x), dried, and evaporated. The residue was purified by prep.

[0466] TLC (5% MeOH in DCM) to 4-(3,3-difluoro-propyl)-pyridine-2-carboxylic acid methyl ester (137 mg, 45%): $^1$H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, J = 5.1, 1), 8.00-7.98 (m, 1), 7.33-7.29 (m, 1), 5.85 (dddd, J = 4.1, 4.1, 56.4, 56.4, 1), 3.99 (s, 3), 2.90-2.83 (m, 2), 2.28-2.09 (m, 2); MS (ESPOS): 216.4 $[M+H]^+$.

[0467] To a solution of 4-(3,3-difluoro-propyl)-pyridine-2-carboxylic acid methyl ester (130 mg, 0.6 mmol) (or compound **14c** ($R^9$ = 2,2-difluoroethyl) prepared in the previous steps) in MeOH (3 mL) and water (3 mL) were added conc. HCl (0.25 mL, 3.0 mmol, 5 equiv) and platinum oxide (65 mg). The mixture was purged and charged with hydrogen (1 atm) and stirred overnight. The platinum oxide was removed by filtration and the filtrate was evaporated to give a clear syrup. To the above residue were added 2N NaOH (1.21 mL) and t-butyl alcohol (0.7 mL). The mixture was stirred at rt for 2 hrs. Then di-t-butyl dicarbonate (0.16 g, 0.73 mmol) was added. The mixture was stirred at rt overnight. The solvent was removed under vacuum. The residue was diluted with water (10 mL), was washed with ether (20 mL). The aqueous layer was acidified with 2N HCl to pH = 2.0, and extracted with ethyl acetate (2x). The combined organic layers were dried and concentrated to give 4-(3,3-Difluoro-propyl)-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester as a clear syrup (163 mg, 88 %)

[0468] $^1$H NMR (300 MHz, $CDCl_3$) δ 5.77 (dddd, J = 4.2, 4.2, 56.6, 56.6, 1), 4.34 (t, J = 6.4, 1), 3.62-3.50 (m, 1), 3.41-3.30 (m, 1), 2.05-1.96 (m, 1), 1.92-1.73 (m, 4), 1.70-1.60 (m, 1), 1.52-1.32 (m, 3), 1.43 (s, 9); MS (ESPOS): 330.5 $[M + Na]^+$; MS (ESNEG): 306.5 $[M-H]^-$.

[0469] To a mixture of the HCl salt of compound **2b** ($R^1$=Me, $R^2$=Me) (140 mg, 0.49 mmol, 1 equiv) in dry DMF (1.2 mL) at 0 °C was added triethylamine (0.34 mL, 2.43 mmol, 5 equiv), followed by the addition of BSTFA (0.20 mL, 0.74 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C for 10 minutes, and then was stirred at rt for 50 minutes. To the reaction mixture were added the 4-(3,3-Difluoro-propyl)-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester (153 mg, 0.50 mmol, 1.0 equiv) and HATU (235 mg, 0.62 mmol, 1.26 equiv). The reaction mixture was stirred at rt for 3 h. The reaction mixture was evaporated to dryness, taken up in ethyl acetate, washed with 10% citric acid (1x), water (1x), sat. $NaHCO_3$ (1x) and brine. The organic

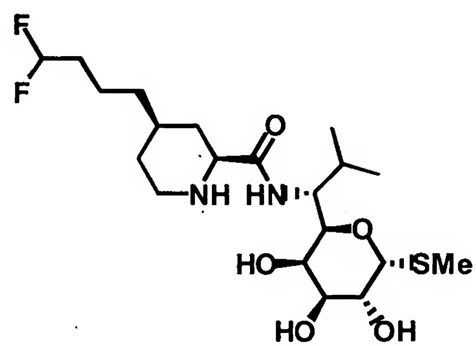
layer was dried over $Na_2SO_4$ and evaporated to give a pink syrup which was used without purification.

[0470] To a solution of the above syrup in DCM (15 mL) with methyl sulfide (0.33 mL) were added trifluoroacetic acid (5 mL) and water (0.33 mL). The reaction mixture was stirred at rt for 1 h. The solvent was removed under vacuum and co-evaporated with toluene twice. The residue was purified by chromatography to provide the title compound (lower isomer, 93 mg, 43%) as a white solid.

[0471] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.90 (dddd, J = 4.2, 4.2, 56.7, 56.7, 1), 5.24 (d, J = 6, 1), 4.21 (dd, J = 3.5, 9.8, 1), 4.11-4.04 (m, 2), 3.84-3.77 (m, 2), 3.51 (dd, J = 3.2, 10.3, 1), 3.45-3.37 (m, 1), 3.07-2.98 (m, 1), 2.23-2.12 (m, 2), 2.11 (s, 3), 1.98-1.66 (m, 4), 1.52-1.26 (m, 4), 0.94-0.88 (m, 6). MS (ESPOS): 441.7 $[M+H]^+$.

## Example 42

### Preparation of 1-(4-(4,4-difluorobut-1-yl)piperid-6-yl)-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide




[0472] To a solution of methyl sulfoxide (0.58 mL, 8.16 mmol, 2.4 equiv) in dichloromethane (1.8 mL) at –72 °C was added a 2 M solution of oxalyl chloride in dichloromethane (2.04 mL, 4.08 mmol, 1.2 equiv) over a period of 1 minute. The mixture was stirred at –72 °C for 25 minutes, followed by the dropwise addition of a solution of the alcohol **14c** ($R^9$=4-hydroxybutyl), prepared using the procedures in Method R, (0.71 g, 3.4 mmol, 1 equiv) in dichloromethane (4.8 mL) over a period of 2 minutes. The reaction mixture was stirred at –72 °C for 25 minutes, then warmed to –50 °C and stirred for an additional 2 h. Triethylamine (1.89 mL, 13.6 mmol, 4.0 equiv) was added and stirred at –50 °C for 25 minutes. The mixture was diluted with ethyl acetate, washed with water (1x), sat. aqueous $NaHCO_3$ (1x),

brine (1x), dried, evaporated and co-evaporated with anhydrous toluene to give aldehyde 4-(4-oxo-butyl)-pyridine-2-carboxylic acid methyl ester as an oil (0.66 mg, 94%).

**[0473]** $^1$H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1), 8.62 (d, J = 5.1, 1), 7.97 (s, 1), 7.29 (d, J = 5.1, 1), 3.99 (s, 3), 2.72 (t, J = 7.8, 2), 2.50 (t, J = 7.2, 2), 2.04-1.93 (m, 2); MS (ESPOS): 230.4 $[M + Na]^+$.

**[0474]** To a solution of 4-(4-oxo-butyl)-pyridine-2-carboxylic acid methyl ester (0.66 g, 3.19 mmol, 1 equiv) in DCM (12 mL) at -78 °C was added DAST (1.69 mL, 12.75 mmol, 4 equiv). The mixture was warmed to rt and stirred overnight. The mixture was diluted with dichloromethane, washed with sat. aqueous $NaHCO_3$ (1x), brine (1x), dried, evaporated. The residue was purified by chromatography to provide 4-(4,4-difluorobutyl)-pyridine-2-carboxylic acid methyl ester (0.54 g, 74%).

**[0475]** $^1$H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, J = 5.1, 1), 7.97-7.95 (m, 1), 7.29-7.26 (m, 1), 5.81 (dddd, J = 3.9, 3.9, 56.6, 56.6, 1), 3.98 (s, 3), 2.74 (t, J = 7.2, 2), 1.93-1.77 (m, 4). MS (ESPOS): 230.4 $[M+H]^+$, 252.4 $[M + Na]^+$.

**[0476]** To a mixture 4-(4,4-difluorobutyl)-pyridine-2-carboxylic acid methyl ester (0.54 g, 2.36 mmol, 1 equiv) in MeOH (8 mL) and water (8 mL) were added conc. HCl (0.59 mL, 7.07 mmol, 3 equiv) and platinum oxide (0.2 g). The mixture was purged and charged with hydrogen (1 atm) and stirred overnight. The platinum oxide was removed by filtration and the filtrate was evaporated to give a residue:

**[0477]** MS (ESPOS): 236.6 $[M+H]^+$.

**[0478]** To the residue prepared above were added 2N NaOH (4.72 mL) and t-butyl alcohol (2.5 mL). The mixture was stirred at rt for 2 hrs. Then di-t-butyl dicarbonate (0.77 g, 3.54 mmol) was added. The mixture was stirred at rt overnight. The solvent was removed under vacuum. The residue was diluted with water (10 mL), was washed with ether (20 mL). The aqueous layer was acidified with 2N HCl to pH = 2.0, extracted with ethyl acetate (2x). The combined organic layers were dried and concentrated to give 4-(4,4-difluoro-butyl)-piperidine-1, 2-dicarboxylic acid 1-tert-butyl ester (0.67 g, 89 %).

**[0479]** $^1$H NMR (300 MHz, $CDCl_3$) δ 5.77 (dddd, J = 4.3, 4.3, 56.8, 56.8, 1), 4.30 (t, J = 6.8, 1), 3.58-3.47 (m, 1), 3.41-3.31 (m, 1), 2.05-1.96 (m, 1), 1.87-1.68 (m, 4), 1.65-1.56 (m, 1), 1.51-1.30 (m, 5), 1.43 (s, 9); MS (ESPOS): 344.5 $[M + Na]^+$.

**[0480]** To a mixture of the HCl salt of compound **2b** ($R^1$=Me, $R^2$=Me) (153 mg, 0.53 mmol, 1 equiv) in dry DMF (1.3 mL) at 0°C was added triethylamine (0.37 mL, 2.66 mmol, 5 equiv), followed by the addition of BSTFA (0.21 mL, 0.80 mmol, 1.5 equiv). The reaction mixture was

stirred at 0°C for 10 minutes, and then was stirred at rt for 50 minutes. To the reaction mixture were added the 4-(4,4-difluoro-butyl)-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester (196 mg, 0.61 mmol, 1.15 equiv) and HATU (293 mg, 0.77 mmol, 1.45 equiv). The reaction mixture was stirred at rt for 3 h. The reaction mixture was evaporated to dryness, taken up in ethyl acetate, washed with 10% citric acid (1x), water (1x), sat. $NaHCO_3$ (1x) and brine. The organic layer was dried over $Na_2SO_4$ and evaporated to give a syrup. The residue was dissolved in methanol (20 mL), then dried and washed Dowex resin (100 mg) was added. The mixture was stirred at rt for 30 minutes, and filtered. The filtrate was concentrated to give a clear syrup, which was purified by chromatography to give a clear syrup (0.25g, 85 %).

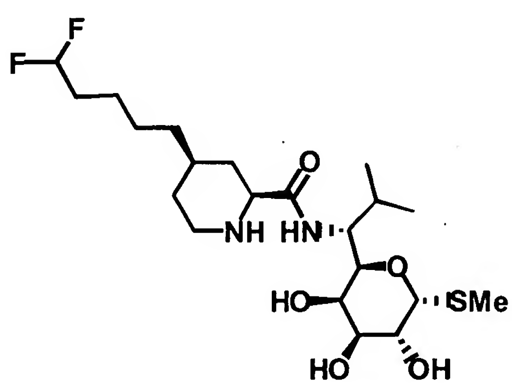
[0481] MS (ESPOS): 555.8 $[M+H]^+$.

[0482] To a solution of the above syrup in DCM (15 mL) with methyl sulfide (0.33 mL) were added trifluoroacetic acid (5 mL) and water (0.33 mL). The reaction mixture was stirred at rt for 1 h. The solvent was removed under vacuum and co-evaporated with toluene twice. The residue was purified by chromatography to provide the title compound (lower isomer, 70 mg, 34%) as a white solid.

[0483] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.88 (dddd, J = 4.4, 4.4, 57, 57, 1), 5.24 (d, J = 5.4, 1), 4.20 (dd, J = 3.2, 10.1, 1), 4.12-4.03 (m, 2), 3.90-3.80 (m, 2), 3.52 (dd, J = 3.5, 10.3, 1), 3.46-3.39 (m, 1), 3.09-2.98 (m, 1), 2.25-2.12 (m, 2), 2.11 (s, 3), 1.98-1.67 (m, 4), 1.56-1.30 (m, 6), 0.95-0.87 (m, 6); MS (ESPOS): 455.7 $[M+H]^+$.

## Example 43

**Preparation of 1-(4-(5,5-difluoropent-1-yl)piperid-6-yl)-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide**






pa-858557

[0484] Method R is used to prepare compound **14c** ($R^{9'}$ = 5-hydroxypentyl) (To a dry flask was added compound **14a** (2 g, 7.60 mmol, 1 equiv), triphenylphosphine (159.4 mg, 0.61 mmol, 0.08 equiv), copper (I) iodide (115.8 mg, 0.61 mmol, 0.08 equiv), palladium acetate (68.2 mg, 0.30 mmol, 0.04 equiv) and triethylamine (28 mL). The mixture was deaerated with nitrogen, followed by addition of 4-pentyn-1-ol (1.28 g, 15.21 mmol, 2 equiv). The mixture was stirred at rt overnight. The solvent was removed under vacuum to give a dark residue. The residue was purified by chromatography to give **14b** ($R^{9'}$ = 5-hydroxypent-1-yn-yl).

[0485] To a solution of **14b** ($R^{9'}$ = 5-hydroxypent-1-yn-yl) in methanol (60 mL) was added 10% palladium on carbon (0.62 g). The mixture was purged and charged with hydrogen (1 atm) and stirred at rt overnight. The palladium was removed by filtration and the filtrate was concentrated to give a yellow oil **14c** ($R^9$ = 5-hydroxypentyl) (1.34 g, 79 %).

[0486] $^1$H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, J = 4.8, 1), 7.97 (s, 1), 7.31 (dd, J = 1.6, 5, 1), 3.99 (s, 3), 3.63 (t, J = 6.5, 2), 2.70 (t, J = 7.7, 2), 1.74-1.53 (m, 4), 1.46-1.34 (m, 2).

[0487] To a solution of methyl sulfoxide (0.46 mL, 6.42 mmol, 2.6 equiv) in dichloromethane (1.4 mL) at –72 °C was added a 2 M solution of oxalyl chloride in dichloromethane (1.61 mL, 3.21 mmol, 1.3 equiv) over a period of 1 minute. The mixture was stirred at –72 °C for 25 minutes, followed by the dropwise addition of a solution of pyridine **14c** ($R^9$ = 5-hydroxypentyl) (0.55 g, 2.47 mmol, 1 equiv) in dichloromethane (3.8 mL) over a period of 2 minutes. The reaction mixture was stirred at –72 °C for 25 minutes, then warmed to –50 °C and stirred for an additional 2 h. Triethylamine (1.48 mL, 10.7 mmol, 4.33 equiv) was added and stirred at –50 °C for 25 minutes. The mixture was diluted with ethyl acetate, washed with water (2x), sat. aqueous $NaHCO_3$ (1x), brine (1x), dried, evaporated and co-evaporated with anhydrous toluene to 4-(5-oxo-pentyl)-pyridine-2-carboxylic acid methyl ester (0.48 mg, 88 %).

[0488] $^1$H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, J = 1.4, 1), 8.61 (d, J = 5.1, 1), 7.97-7.95 (m, 1), 7.28 (dd, J = 1.7, 5, 1), 3.99 (s, 3), 2.73-2.67 (m, 2), 2.50-2.44 (m, 2), 1.71-1.63 (m, 4).

[0489] To a solution of the to 4-(5-oxo-pentyl)-pyridine-2-carboxylic acid methyl ester oil (0.48 g, 2.19 mmol, 1 equiv) in DCM (8 mL) at -78°C was added DAST (1.41 g, 8.74 mmol, 4 equiv). The mixture was warmed to rt and stirred overnight. The mixture was diluted with dichloromethane, washed with sat. aqueous $NaHCO_3$ (1x), dried, and evaporated. The residue was purified by chromatography to 4-(5,5-Difluoro-pentyl)-pyridine-2-carboxylic acid methyl ester (278 mg, 52 %)

[0490] $^1$H NMR (300 MHz, $CDCl_3$) δ 8.61 (dd, J = 0.6, 4.8, 1), 7.97-7.95 (m, 1), 7.28 (dd, J = 1.5, 4.8, 1), 5.78 (dddd, J = 4.3, 4.3, 57, 57, 1), 3.99 (s, 3), 2.70 (t, J = 7.7, 2), 1.94-1.66 (m, 4), 1.55-1.43 (m, 2).

[0491] MS (ESPOS): 244.2 $[M+H]^+$

[0492] To a mixture of 4-(5,5-difluoro-pentyl)-pyridine-2-carboxylic acid methyl ester (278 mg, 1.14 mmol) in MeOH (5 mL) and water (5 mL) were added conc. HCl (0.286 mL, 3.43 mmol, 3 equiv) and platinum oxide (140 mg). The mixture was purged and charged with hydrogen (1 atm) and stirred overnight. The platinum oxide was removed by filtration and the filtrate was evaporated to 4-(5,5-difluoro-pentyl)-piperidine-2-carboxylic acid 2-methyl ester.

[0493] MS (ESPOS): 250.2 $[M+H]^+$.

[0494] To the above residue 4-(5,5-difluoro-pentyl)-piperidine-2-carboxylic acid-2-methyl ester were added 2N NaOH (2.3 mL) and t-butyl alcohol (1.2 mL). The mixture was stirred at rt for 2 hrs. Then di-t-butyl dicarbonate (0.37 g, 1.72 mmol) was added. The mixture was stirred at rt overnight. The solvent was removed under vacuum. The residue was diluted with water, was washed with ether. The aqueous layer was acidified with 2N HCl to pH = 2.0, extracted with ethyl acetate (2x). The combined organic layers were dried and concentrated to 4-(5,5-Difluoro-pentyl)-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester (310 mg, 81 %).

[0495] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.84 (dddd, J = 4.5, 4.5, 57, 57, 1), 4.31 (t, J = 6.3, 1), 3.65-3.56 (m, 1), 3.35-3.25 (m, 1), 2.03-1.63 (m, 5), 1.48-1.30 (m, 8), 1.43 (s, 9).

[0496] To a mixture of the HCl salt of compound **2b** ($R^1$=Me, $R^2$=Me) (223.7 mg, 0.78 mmol, 1 equiv) in dry DMF (1.9 mL) at 0°C was added triethylamine (0.54 mL, 3.89 mmol, 5 equiv), followed by the addition of BSTFA (0.31 mL, 1.17 mmol, 1.5 equiv). The reaction mixture was stirred at 0°C for 10 minutes, and then was stirred at rt for 50 minutes. To the reaction mixture were added 4-(5,5-difluoro-pentyl)-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester (272 mg, 0.81 mmol, 1.05 equiv) and HATU (391 mg, 1.03 mmol, 1.32 equiv). The reaction mixture was stirred at rt for 3 h. The reaction mixture was evaporated to dryness, taken up in ethyl acetate, washed with 10% citric acid (1x), water (1x), sat. $NaHCO_3$ (1x) and brine. The organic layer was dried over $Na_2SO_4$ and evaporated to give a residue. The residue was dissolved in methanol (30 mL), then dry and washed Dowex resin (150 mg) was added. The mixture was stirred at rt for 1 h and filtered. The filtrate was concentrated to give a clear syrup, which was purified by chromatography to give a clear syrup (0.26 g, 72 %).

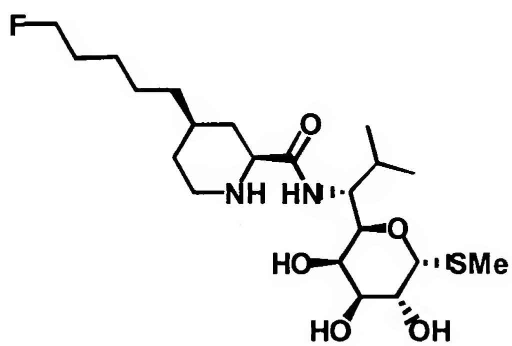
[0497] To a solution of the above syrup in DCM (15 mL) with methyl sulfide (0.33 mL) were added trifluoroacetic acid (5 mL) and water (0.33 mL). The reaction mixture was stirred at

rt for 1 h. The solvent was removed under vacuum and co-evaporated with toluene twice. The residue was purified by chromatography to provide the title compound (lower isomer, 40 mg, 15 %) as a white solid.

[0498] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.86 (dddd, J = 4.5, 4.5, 57, 57, 1), 5.24 (d, J = 5.7, 1), 4.21 (dd, J = 3.3, 9.9, 1), 4.11-4.04 (m, 2), 3.86-3.78 (m, 2), 3.51 (dd, J = 3.5, 10.4, 1), 3.47-3.38 (m, 1), 3.07-2.97 (m, 1), 2.23-2.12 (m, 2), 2.11 (s, 3), 1.98-1.64 (m, 4), 1.50-1.27 (m, 8), 0.94-0.87 (m, 6); MS (ESPOS): 469.4 $[M+H]^+$.

## Example 44

### Preparation of 1-(4-(5-fluoropent-1-yl)piperid-6-yl)-N-{ 1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide



[0499] To a solution of compound **14c** ($R^9$= 5-hydroxypentyl) (0.66 g, 2.96 mmol, 1 equiv), prepared as described in Method R and in the synthesis of Example **47,** in DCM (11 mL) at -78°C was added DAST (1.91 g, 11.85 mmol, 4 equiv). The mixture was warmed to rt and stirred overnight. The mixture was diluted with dichloromethane, washed with sat. aqueous $NaHCO_3$ (1x), dried, and evaporated. The residue was purified by chromatography to give 4-(5-fluoro-pentyl)-pyridine-2-carboxylic acid methyl ester (254 mg, 38 %)

[0500] $^1$H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, J = 4.8, 1), 7.97 (d, J = 1.2, 1), 7.30 (dd, J = 1.7, 5, 1), 4.50 (t, J = 5.9, 1), 4.34 (t, J = 6, 1), 3.99 (s, 3), 2.70 (t, J = 7.7, 2), 1.80-1.62 (m, 4), 1.50-1.41 (m, 2).

[0501] To a mixture of 4-(5-fluoro-pentyl)-pyridine-2-carboxylic acid methyl ester (254 mg, 1.13 mmol) in MeOH (5 mL) and water (5 mL) were added conc. HCl (0.28 mL, 3.39 mmol, 3 equiv) and platinum oxide (130 mg). The mixture was purged and charged with hydrogen (1

atm) and stirred overnight. The platinum oxide was removed by filtration and the filtrate was evaporated to give 4-(5-fluoro-pentyl)-piperidine-2-carboxylic acid 2-methyl ester.

**[0502]** MS (ESPOS): 232.4 $[M+H]^+$.

**[0503]** To 4-(5-fluoro-pentyl)-piperidine-2-carboxylic acid 2-methyl ester was added 2N NaOH (2.43 mL) and t-butyl alcohol (1.3 mL). The mixture was stirred at rt for 2 hrs. Then di-t-butyl dicarbonate (0.40 g, 1.82 mmol) was added. The mixture was stirred at rt overnight. The solvent was removed under vacuum. The residue was diluted with water, was washed with ether. The aqueous layer was acidified with 2N HCl to pH = 2.0, extracted with ethyl acetate (2x). The combined organic layers were dried and concentrated to give 4-(5-fluoro-pentyl)-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester as a syrup (254 mg, 71 %).

**[0504]** $^1$H NMR (300 MHz, $CDCl_3$) δ 4.52-4.06 (m, 3), 3.55-3.30 (m, 2), 2.03-1.94 (m, 1), 1.81-1.54 (m, 4), 1.45-1.20 (m, 8), 1.43 (s, 9). MS (ESPOS): 218.3 $[M + Na - Boc]^+$

**[0505]** To a mixture of the HCl salt of compound **2b** ($R^1$=Me, $R^2$=Me) (213.8 mg, 0.74 mmol, 1 equiv) in dry DMF (1.8 mL) at 0 °C was added triethylamine (0.52 mL, 3.72 mmol, 5 equiv), followed by the addition of BSTFA (0.30 mL, 1.12 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C for 10 minutes, and then was stirred at rt for 50 minutes. To the reaction mixture were added the 4-(5-fluoro-pentyl)-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester as a syrup (244 mg, 0.77 mmol, 1.04 equiv) and HATU (370 mg, 0.97 mmol, 1.31 equiv). The reaction mixture was stirred at rt for 3 h. The reaction mixture was evaporated to dryness, taken up in ethyl acetate, washed with 10% citric acid (1x), water (1x), sat. $NaHCO_3$ (1x) and brine. The organic layer was dried over $Na_2SO_4$ and evaporated to give a residue. The residue was dissolved in methanol (30 mL), then dry and washed Dowex resin (140 mg) was added. The mixture was stirred at rt for 1 h and filtered. The filtrate was concentrated to give a clear syrup, which was purified by chromatography to give a clear syrup (212 mg, 52 %).

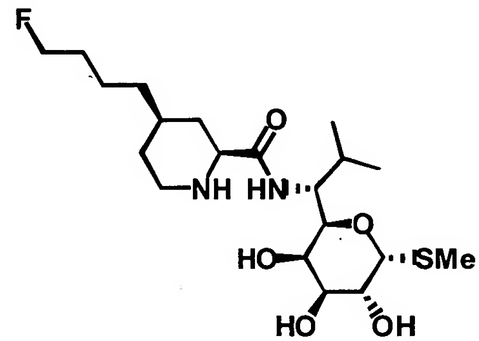
**[0506]** To a solution of the above syrup in DCM (15 mL) with methyl sulfide (0.33 mL) were added trifluoroacetic acid (5 mL) and water (0.33 mL). The reaction mixture was stirred at rt for 1 h. The solvent was removed under vacuum and co-evaporated with toluene twice. The residue was purified by chromatography to provide the title compound (lower isomer, 40 mg, 17 %) as a white solid.

**[0507]** $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, J = 5.7, 1), 4.49 (t, J = 5.9, 1), 4.33 (t, J = 6, 1), 4.20 (dd, J = 3.5, 10.1, 1), 4.11-4.04 (m, 2), 3.83-3.77 (m, 2), 3.51 (dd, J = 3.3, 10.2, 1), 3.44-3.36 (m, 1), 3.06-2.94 (m, 1), 2.23-2.13 (m, 2), 2.11 (s, 3), 1.98-1.88 (m, 1), 1.77-1.59 (m, 3), 1.45-1.27 (m, 8), 0.94-0.87 (m, 6).

[0508] MS (ESPOS): 451.4 $[M+H]^+$

## Example 45

### Preparation of 1-(4-(4-fluorobut-1-yl)piperid-6-yl)-N-{ 1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide



[0509] To a solution of compound **14c** ($R^9$ = 4-hydroxybutyl) (0.76 g, 3.62 mmol, 1 equiv), prepared as described in Method R and in the synthesis of Example **47,** in DCM (14 mL) at -78 °C was added DAST (1.9 mL, 14.47 mmol, 4 equiv). The mixture was warmed to rt and stirred overnight. The mixture was diluted with dichloromethane, washed with sat. aqueous $NaHCO_3$ (1x), brine (1x), dried, evaporated. The residue was purified by chromatography to provide 4-(4-Fluoro-butyl)-pyridine-2-carboxylic acid methyl ester as a yellow oil (0.24 g, 31 %).

[0510] $^1$H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, J = 4.8, 1), 7.92 (d, J = 1.2, 1), 7.27-7.23 (m, 1), 4.49 (t, J = 5.6, 1), 4.33 (t, J = 5.6, 1), 3.94 (s, 3), 2.69 (t, J = 7.5, 2), 1.79-1.59 (m, 4).

[0511] To a mixture of 4-(4-fluoro-butyl)-pyridine-2-carboxylic acid methyl ester (0.24 g) in THF (3 mL) and water (1 mL) was added lithium hydroxide monohydrate (71.3 mg, 1.7 mmol, 1.5 equiv). The mixture was stirred at rt overnight and diluted with methanol (20 mL). Then $H^+$ resin was added and the mixture was shaken for 10 minutes. The resin was washed with methanol (1x), 1:1 acetonitrile/water (1x), and acetonitrile (1x). The product was eluted with 5% TEA in methanol (4x) and acetonitrile (1x). The combined organic solvents were evaporated and co-evaporated with toluene to provide 4-(4-Fluoro-butyl)-pyridine-2-carboxylic acid (0.22 g, 65 %).

[0512] $^1$H NMR (300 MHz, $CD_3OD$) δ 8.46 (d, J = 4.8, 1), 7.95 (s, 1), 7.39-7.35 (m, 1), 4.52 (t, J = 5.6, 1), 4.36 (t, J = 5.9, 1), 3.22 (q, J = 7.3, 2.5H, TEA), 2.77 (t, J = 7.5, 2), 1.84-1.62 (m, 4), 1.28 (t, J = 7.2, 3.8H, TEA).

[0513] To a solution of 4-(4-fluoro-butyl)-pyridine-2-carboxylic acid (0.22 g, 0.73 mmol, 1 equiv) in dry acetonitrile (4 mL) at 0°C was added triethylamine (74 mg, 0.73 mmol, 1 equiv), followed by the addition of isobutyl chloroformate (100 mg, 0.73 mmol, 1 equiv). The reaction mixture was stirred at 0°C for 15 minutes, and then was stirred at 4°C for 2 h. To the reaction mixture was added a solution of the HCl salt of compound **2b** ($R^1$=Me, $R^2$=Me) (263 mg, 0.91 mmol, 1.25 equiv) and triethylamine (93 mg, 0.91 mmol, 1.25 equiv) in a 1:1 acetone/water (4 mL). The reaction mixture was stirred at 4 °C overnight. The reaction mixture was evaporated to dryness, taken up in DCM, washed with sat. $NaHCO_3$ (1x). The organic layer was dried over $Na_2SO_4$ and evaporated. The residue was purified by chromatography to give a clear solid (110 mg, 35 %).

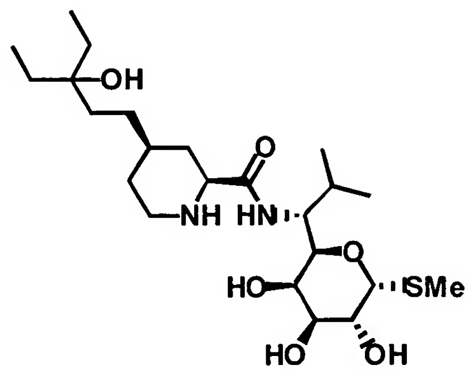
[0514] To a solution of the above solid (110 mg, 0.25 mmol, 1 equiv) in MeOH (6 mL) and water (4 mL) were added conc. HCl (20.2 μL, 0.24 mmol, 0.95 equiv) and platinum oxide (220 mg). The mixture was purged and charged with hydrogen (65 psi) and shaken overnight. The platinum oxide was removed by filtration and the filtrate was evaporated to give a residue, which was purified by chromatography to provide the title compound (lower isomer, 33 mg, 30%) as a white solid.

[0515] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.25 (d, J = 5.4, 1), 4.51 (t, J = 6, 1), 4.35 (t, J = 5.9, 1), 4.21 (dd, J = 3.3, 10.2, 1), 4.10-4.04 (m, 2), 3.93-3.80 (m, 2), 3.52 (dd, J = 3.3, 10.2, 1), 3.46-3.38 (m, 1), 3.11-2.98 (m, 1), 2.26-2.13 (m, 2), 2.11 (s, 3), 2.00-1.92 (m, 1), 1.80-1.60 (m, 3), 1.54-1.27 (m, 6), 0.95-0.87 (m, 6).

[0516] MS (ESPOS): 437.4 $[M+H]^+$

**Example 46**

**Preparation of 1-(4-(3-ethyl-3-hydroxypent-1-yl)piperid-6-yl)-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide**



[0517] To a dry flask was added compound **13b** ($R^1$=Me, $R^2$=Me, and $R^3$=H) made using Method Q (130 mg, 0.27 mmol, 1 equiv), triphenylphosphine (45.3 mg, 0.17 mmol, 0.64 equiv), copper (I) iodide (32.9 mg, 0.17 mmol, 0.64 equiv), palladium acetate (19.4 mg, 0.086 mmol, 0.32 equiv) and triethylamine (1.5 mL). The mixture was deaerated with nitrogen, followed by addition of 3-ethyl-1-pentyn-3-ol (174 μL, 1.35 mmol, 5 equiv). The mixture was stirred at 50 °C overnight. The solvent was removed under vacuum to give a dark residue. The residue was purified by chromatography to give **13c** ($R^1$=Me, $R^2$=Me, $R^3$=H, $R^9$=3-Ethyl-3-hydroxy-pent-1-ynyl).

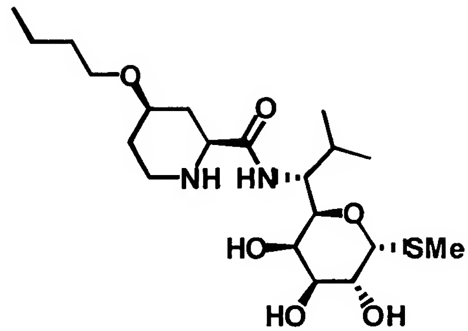
[0518] MS (ESPOS): 467.7 $[M+H]^+$; MS (ESNEG): 465.5 $[M-H]^-$.

[0519] To a mixture of the above syrup in MeOH (12 mL) and water (8 mL) were added platinum oxide (300 mg) and conc. HCl (26 μL). The mixture was purged and charged with hydrogen (65 psi) and shaken overnight. The platinum oxide was removed by filtration and the filtrate was evaporated. The residue was purified by chromatography to give the title compound as a white solid (19 mg, 15 %).

[0520] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, J = 5.7, 1), 4.17 (dd, J = 3.1, 10.0, 1), 4.10-4.02 (m, 2), 3.80 (d, J = 3, 1), 3.53-3.48 (m, 1), 3.42-3.35 (m, 1), 3.23-3.15 (m, 1), 2.75-2.64 (m, 1), 2.22-2.11 (m, 1), 2.10 (s, 3), 2.04-1.97 (m, 1), 1.80-1.72 (m, 1), 1.50-1.40 (m, 6), 1.31-1.06 (m, 5), 0.94-0.80 (m, 12); MS (ESPOS): 477.8 $[M+H]^+$; MS (ESNEG): 475.6 $[M-H]^-$.

## Example 47

**Preparation of 1-(4-butoxypiperid-6-yl)-N-{ 1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide**



[0521] To trimethylsilyl cyanide (5.2 g, 52 mmol), 4-benzyloxy-pyridine 1-oxide (8.8 g, 44 mmol) in DCM (20 mL) was added, followed by dimethylcarbamoyl chloride (5.6 g, 52 mmol) in DCM (10 mL), dropwise, stirred at room temperature overnight. Sodium bicarbonate (100 mL, 10%) was added, stirred for 10 minutes and extracted twice with DCM (50 mL). The combined organic layer was dried over magnesium sulfate, solvent was removed to obtain the product, compound **10a** ($R^9$ = Benzyloxy) (10.5 g, 100%).

[0522] $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.34 (d, J=5.7, 1), 7.24 (m, 5), 7.11 (t, J=2.4, 1), 6.90 (dd, J=5.7, 2.4, 1), MS (ESPOS): 211[M+H]$^+$.

[0523] Compound **10a** ($R^9$ = Benzyloxy) (5 g, 23 mmol) was dissolved in HCl (6N, 70 mL) and refluxed overnight. The crude product 4-hydroxypyridine-2-carboxylic acid, compound **10b** ($R^9$ = hydroxy) obtained on removal of HCl was crystallized from acetonitrile (2.6 g, 80%).

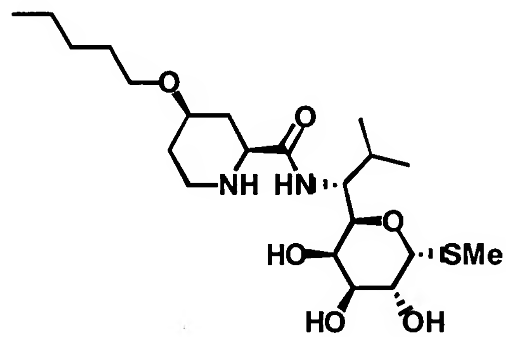
[0524] $^1H$ NMR (300 MHz, $CD_3OD$) δ 8.55 (d, J=6.6, 1), 7.78 (d, J=3.0, 1), 6.90 (dd, J=2.7, 6.9, 1), MS (ESNEG): 138 [M-H]$^-$.

[0525] The synthesis of title compound was completed using the synthetic sequence found in Method S starting from 4-hydroxypyridine-2-carboxylic acid, as prepared above.

[0526] $^1H$ NMR (300 MHz, $CD_3OD$) δ 5.25 (d, J=5.4, 1), 4.22 (dd, J=10.2; 3.3, 1), 4.08 (m, 2), 3.81 (d, J=3.0, 1), 3.70 (m, 1), 3.54 (m, 4), 3.43 (m, 2), 2.90 (m, 1), 2.41 (m, 1), 2.19 (m, 1), 2.10 (s, 3) 1.45 (m, 6), 0.92 (m, 9); MS (ESPOS): 435 [M+H]$^+$.

## Example 48

### Preparation of 1-(4-pentoxypiperid-6-yl)-N-{ 1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide



[0527] The title compound was made using the synthetic sequence found in Method S starting from 4-hydroxypyridine-2-carboxylic acid **10b** ($R^9$ = hydroxy) substituting n-pentyl bromide as the alkylating agent.

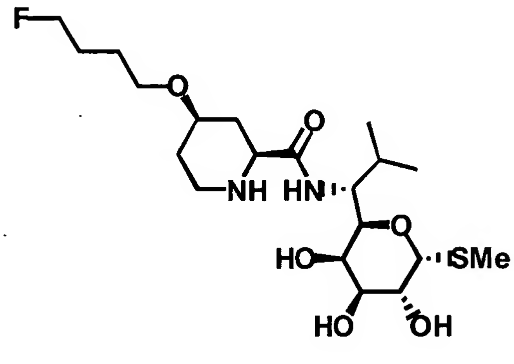
[0528] Compound **15a** ($R^9$ = pentoxy): $^1$H NMR (300 MHz, $CD_3OD$) δ 8.38 (d, J=5.1, 1), 7.64 (s, 1), 7.10 (d, J=3.3, 1), 4.18 (t, J=6.6, 2), 1.85 (m, 2), 1.49 (m, 4), 0.96 (t, J=7.2, 3). MS (ESNEG): 208 $[M-H]^-$.

[0529] Compound **15b** ($R^1$=Me, $R^2$=Me, $R^9$= pentoxy): $^1$H NMR (300 MHz, $CD_3OD$) δ 8.41 (d, J=5.7, 1), 7.61 (d, J=2.4, 1), 7.07 (dd, J=2.4, 5.4, 1), 5.27 (d, J=5.4, 1), 4.05-4.31 (m, 5), 3.85 (d, J=3.0, 1), 3.57 (dd, J=3.3, 7.2, 1), 2.11 (m, 4), 1.81 (m, 2), 1.49 (m, 4), 1.00 (m, 9). MS (ESPOS): 443 $[M+H]^+$.

[0530] Title compound (20 mg, 10%): $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, J=5.7, 1), 4.22 (dd, J=9.9; 3.3, 1), 4.10 (m, 2), 3.76 (m, 3), 3.51 (m, 3), 3.39 (m, 1), 3.02 (m, 2), 2.43 (m, 1), 2.15 (m, 1), 2.10 (s, 3) 1.95 (m, 2), 1.69 (m, 2), 1.53 (m, 2), 1.34 (m, 2), 0.93 (m, 9); MS (ESPOS): 449 $[M+H]^+$.

## Example 49

### Preparation of 1-(4-(4-fluorobutoxy)piperid-6-yl)-N-{ 1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide

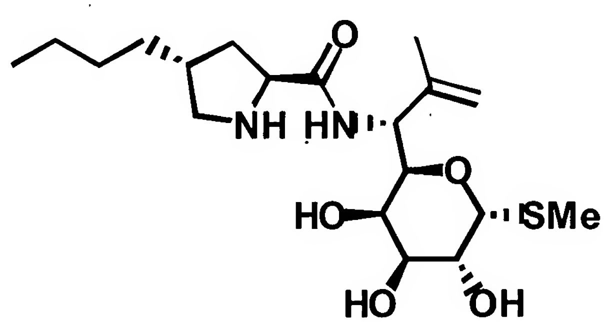


[0531] The title compound was made using the synthetic sequence found in Method S starting from 4-hydroxypyridine-2-carboxylic acid **10b** ($R^9$ = hydroxy) substituting 4-fluorobutyl bromide as the alkylating agent.

[0532] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.25 (d, J=5.7, 1), 4.53 (t, J=5.7, 1), 4.37 (t, J=5.7, 1), 4.21 (dd, J=3.3, 6.6, 1), 4.07 (m, 2), 3.80 (d, J=3.3, 2), 3.60 (m, 5), 2.88 (m, 1), 2.38 (m, 1), 2.18 (m, 1), 2.10 (s, 3) 1.33-1.83 (m, 8), 0.92 (m, 6); MS (ESPOS): 453 $[M+H]^+$.

## Example 50

### Preparation of 1-[4-n-butylprop-1-yl)pyrrolidin-2-yl]-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methyl-allyl}acetamide



[0533] To a solution of Boc 7-Methylene MTL (P=Boc, $R^1$=Me, $R^2$=$CH_2$) prepared from compound **2a** (P=Boc, $R^1$=Me) by Method D (391mg, 1.1 mmol) in a solution of dichloroethane

(10 mL) and dimethylsulfide (0.4 mL, 2.5 mmol) was added, TFA (5 mL) containing water (0.4 mL) and the reaction mixture stirred at rt for 45min. The solvent was removed and the residue evaporated twice from DCE to obtain the crude product. The product was obtained as an HCl salt by precipitation from ethyl acetate (4 mL) at 0 °C by addition of 2M HCl in ether, and dried under vacuum (351mg g, 86%). The white solid product was used in the next reaction without additional purification.

**[0534]** MS (ESPOS): 350 $[M+H]^+$.

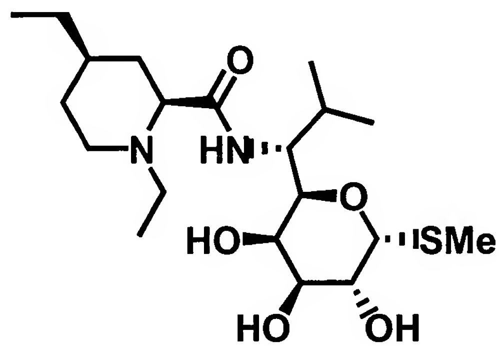
**[0535]** Triethylamine (0.68 mL, 4.9 mmol, 4.0 equiv), followed by BSTFA (0.58 mL, 2.20 mmol, 1.8 equiv), were added to a stirred suspension of compound prepared above (351 mg, 1.22 mmol, 1 equiv) in anhydrous DMF (5 mL) at 0 °C and under nitrogen. The resulting mixture was stirred at 0 °C for 10 min, and then at rt for 50 min. The resulting solution was cooled to 0 °C and a solution of compound **7d** ($R^9$=n-butyl) prepared by Method K (400 mg, 1.47 mmol, 1.2 equiv) in anhydrous DMF (5 mL) was added, followed by solid HATU (741 mg, 1.95 mmol, 1.6 equiv). The reaction mixture was allowed to warm to rt and after 2h the reaction solution was evaporated to dryness under vacuum. The residual oil obtained was diluted with EtOAc (200 mL), washed sequentially with 10% citric acid , 1:1 saturated aqueous $NaHCO_3$, water, and brine dried over $Na_2SO_4$, and evaporated to dryness.

**[0536]** To a solution of 50mg crude coupling product in 1,2-dichloroethane (6 mL), was added dimethylsulfide (200 $\mu$L), followed by TFA (11.5 mL), and water (768 $\mu$L). The resulting mixture was stirred at rt for 1h, evaporated to a minimal volume, diluted with DCE (3 x 10 mL), and evaporated to dryness. The residue was purified by column chromatography 8% to 12% 0.25M methanolic ammonia in dichloromethane to provide the title compound (10.0 mg, 25 %).

**[0537]** $^1$H NMR (300 MHz, $CD_3OD$) δ 5.22 (d, J = 5.8, 1), 5.00 (s, 1), 4.95 (s, 1), 4.58 (d, J = 8.8, 1) 4.19 (d, J = 8.8, 1), 4.09 (dd, J = 5.8, 10.1, 1) 3.85-3.77 (m, 2), 3.57-3.52 (m, 1), 3.26-3.29 (m, 1), 2.59-2.53 (m, 1), 2.10-1.98 (m, 4), 1.80 (s, 3), 1.36-1.51-1.11 (m, 7), 0.91(t, , J=6.9, 3); MS (ESPOS): 403.6 $[M+H]^+$.

## Example 51

### Preparation of 1-( 4-ethyl-N-ethyl-piperid-6-yl)-N-{ 1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide

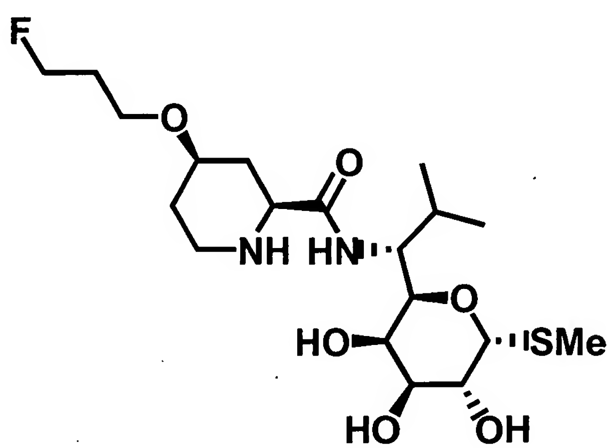


[0538] To the product of Example 1 (30 mg, 0.07 mmol) in DMF (1 mL), DIEA (43 mg, 0.35 mmol) was added at room temperature and stirred overnight. Then removed the solvent and the resulting product was purified by column chromatography using 20% MeOH in DCM to obtain the title compound (20 mg, 66%) as a white powder.

[0539] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, J = 6.0, 1), 4.26 (dd, J=3.6, 9.6, 1), 3.79 (d, J = 3.0, 1), 3.55 (dd, J=3.3, 10.2, 1) 2.85 (m, 2), 2.13 (m, 4), 1.37 (m, 12), 0.94 (m, 9); MS (ESPOS): 420 $[M+H]^+$.

## Example 52

### Preparation of 1-(4-(3-fluoropropoxy)piperid-6-yl)-N-{ 1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide



[0540] The title compound was made using the synthetic sequence found in Method S starting from 4-hydroxypyridine-2-carboxylic acid substituting 3-fluoropropyl bromide as the alkylating agent.

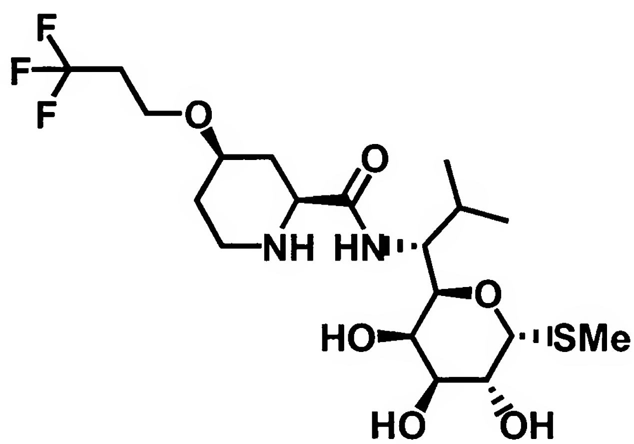
[0541] Compound **15a** ($R^9$ = 3-fluoropropoxy): $^1H$ NMR (300 MHz, $CD_3OD$) δ 8.41 (d, J=5.1, 1), 7.65 (d, J=2.1, 1), 7.14 (dd, J=2.1, 5.7, 1), 4.59 (m, 2), 4.24 (t, J=6.0, 2), 1.91 (m, 2). MS (ESNEG): 212 $[M-H]^-$.

[0542] Compound **15b** ($R^1$=Me, $R^2$=Me, $R^9$ = 3-fluoropropoxy): $^1H$ NMR (300 MHz, $CD_3OD$) δ 8.44 (d, J=5.7, 1), 7.65 (d, J=2.4, 1), 7.12 (dd, J=2.4, 5.7, 1), 5.48 (d, J=5.7, 1), 4.87 (m, 2), 4.30 (m, 2), 4.12 (dd, J=3.0, 10.2, 1), 3.85 (d, J=3.3, 1), 3.56 (dd, J=9.9, 3.3, 1), 2.26 (m, 1), 2.11 (s, 3), 1.37 (m, 4), 1.00 (t, J=5.1, 6). MS (ESPOS): 443 $[M+H]^+$.

[0543] Title compound (60 mg, 31%): $^1H$ NMR (300 MHz, $CD_3OD$) δ 5.25 (d, J=5.7, 1), 4.50 (m, 2), 4.21 (dd, J=3.3, 9.9, 1), 4.06 (m, 2), 3.80 (d, J=2.7, 1), 3.66 (m, 3), 3.59 (m, 1), 3.33 (m, 1), 2.87 (m, 1), 2.41 (m, 1), 2.18 (m, 1), 2.10 (s, 3) 1.91 (m, 4), 1.51 (m, 2), 0.92 (m, 6); MS (ESPOS): 439 $[M+H]^+$.

## Example 53

**Preparation of 1-(4-(3,3,3-trifluoropropoxy)piperid-6-yl)-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide**



[0544] The title compound was made using the synthetic sequence found in general Method S starting from 4-hydroxypyridine-2-carboxylic acid substituting 2-trifluoroethyl bromide as the alkylating agent.

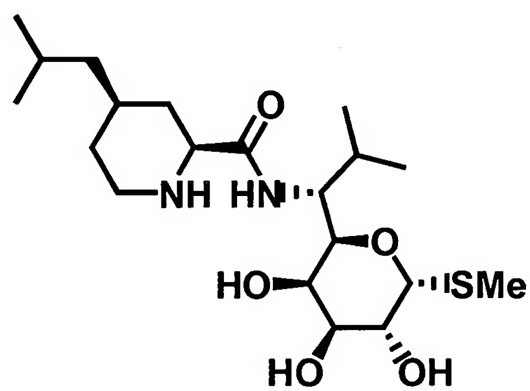
[0545] Compound **15a** ($R^9$ = 3,3,3-trifluoropropoxy): $^1H$ NMR (300 MHz, $CD_3OD$) δ 8.67 (m, 1), 7.92 (s, 1), 7.43 (m, 1), 4.65 (m, 2), 3.01 (m, 2). MS (ESNEG): 234$[M-H]^-$.

[0546] Compound **15b** ($R^1$=Me, $R^2$=Me, $R^9$ = 3,3,3-trifluoropropoxy): $^1$H NMR (300 MHz, $CD_3OD$) δ 8.46 (d, J=6.0, 1), 7.65 (d, J=2.7, 1), 7.13 (dd, J=2.7, 6.0, 1), 5.27 (d, J=5.7, 1), 4.39 (t, J=6.0, 2), 4.30 (m, 2), 4.11 (m, 1), 3.85 (d, J=3.0, 1), 3.57 (dd, J=3.0, 10.2, 1), 2.88 (m, 2), 2.25 (m, 1), 2.11 (s, 3), 1.00 (t, J=6.9, 6). MS (METHOD ESPOS): 469 $[M+H]^+$.

[0547] Title compound (10 mg, 10%): $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, J=5.7, 1), 4.18 (dd, J=3.0, 9.9, 1), 4.15 (m, 2), 3.80 (d, J=3.6, 1), 3.74 (m, 2), 3.52 (dd, J=3.3, 10.2, 2), 3.38 (m, 2), 3.18 (m, 1), 2.66 (m, 1), 2.66 (m, 1), 2.44 (m, 2), 2.22 (m, 1), 2.10 (s, 3) 1.34 (m, 2), 0.91 (d, J=7.2, 6); MS (ESPOS): 475 $[M+H]^+$.

## Example 54

### Preparation of 1-(4-iso-butylpiperid-6-yl)-N-{ 1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide



[0548] 4-Isobutyl-2-cyanopyridine is prepared as follows. To isobutyltriphenylphosphonium iodide (Aldrich) (8 g, 18.5 mmol) in THF (20 mL) at 0 °C, potassium-tert-butoxide (1.8 g, 16 mmol) was added, stirred at room temperature for 1 hr. pyridine-4-carboxlaldehyde (1 g, 9.3 mmol) was added, stirred at room temperature for overnight. Reaction mixture was then poured to water (100 mL) and extracted with EtOAc (100 mL). The product obtained on removal of solvent was purified by column chromatography using 40% EtOAc in hexane as eluent (1.05 g, 84%). To the resulting product (4.2 g, 31.5 mmol), 10% Pd/C (0.4 g) was added and hydrogenated at 1 atm pressure overnight. Removal of solvent and purification on column chromatography using 30% EtOAc in hexanes resulted in 4-isobutylpyridine (3.8 g, 90%).

[0549] The intermediate, 4-isobutylpyridine-2-carboxylic acid, compound **10b**, ($R^9$ =isobutyl) was made by employing Method P. To 4-isobutylpyridine (2 g, 14.8 mmol) in

acetic acid (20 mL), hydrogen peroxide (3.35 g, 30 %, 30 mmol) was added and refluxed overnight. After removing the solvent, the residue was dissolved in DCM dried over magnesium sulfate and taken as such for the next step. To the compound in DCM (10 mL) trimethylsilyl cyanide (1.73 g, 17.4 mmol) and dimethylcarbonyl chloride (1.89 g, 17.4 mmol) was added and stirred at room temperature for 24 hours. Aqueous potassium bicarbonate (100 mL, 10%) was added and extracted twice with DCM (50 mL each). The crude product obtained on removal of solvent was taken in HCl (6N, 100 mL) and refluxed for 24 hours. Removal of acid and purification of crude product by column chromatography using 30% MeOH in DCM resulted in acid **10b** ($R^9$ =isobutyl) (1.5 g, 100%).

**[0550]** $^1$H NMR (300 MHz, $CD_3OD$) δ 8.78 (d, J=5.7, 1), 8.44 (s, 1), 8.13 (d, J=5.7, 1), 2.92 (d, J=7.5, 1), 2.15 (m, 1), 0.98 (d, J=6.6, 6). MS (ESNEG): 178[M-H]$^-$.

**[0551]** To the amine **2b** ($R^1$=Me, $R^2$=Me) (200 mg, 0.79 mmol) in DMF (2ml), TEA (161 mg, 1.6 mmol), BSTFA (614 mg, 2.4 mmol) was added at 0 °C and stirred at room temperature for 1.5 hr. Acid **10b** ($R^9$ = isobutyl) (214 mg, 1.2 mmol) and HATU (368 mg, 1.2 mmol) was added and let stirred at room temperature for 4 hours. DMF was removed and the residue was extracted with EtOAc (50 mL), washed with sodium bicarbonate (10%, 50 mL), brine (50 mL) and dried over magnesium sulfate. The product obtained on removal of solvent was dissolved in methanol (10 mL) and treated with NR-50 resin (300 mg) for 3 hr. After filtering the resin, methanol was removed to obtain the crude product. It was then purified on silica gel column chromatography using 3% MeOH in DCM to obtain compound **11b** ($R^1$=Me, $R^2$=Me, $R^3$=H, $R^9$ =isobutyl) (200 mg, 60%).

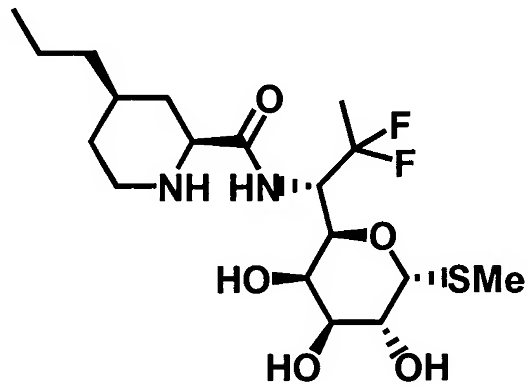
**[0552]** $^1$H NMR (300 MHz, $CD_3OD$) δ 8.41 (d, J=4.8, 1), 8.28 (d, J=9.6, 1), 7.95 (s, 1), 5.35 (d, J=5.4, 1), 4.25 (m, 2), 3.99 (d, J=10.8, 1), 3.78 (d, J=3.6, 1), 3.55 (dd, J=3.6, 10.8, 1), 2.52 (m, 3), 2.15 (s, 3), 1.93 (m, 1), 1.02 (m, 12). MS (ESPOS): 413 [M+H]$^+$.

**[0553]** To compound **11b** ($R^1$=Me, $R^2$=Me, $R^3$=H, $R^9$ =isobutyl) (200 mg, 0.48 mmol) in water (10 mL), AcOH (2 mL) and MeOH (2 mL), $PtO_2$ (200 mg), was added, hydrogenated at 55 psi for 16 hours. After filtering the catalyst, the solvent was removed to obtain the crude material which on purification over silica gel column using 20 % MeOH in DCM as eluent. The lower $R_f$ fraction provided the title compound (70 mg, 34%).

**[0554]** $^1$H NMR (300 MHz, $CD_3OD$) δ 5.25 (d, J=5.7, 1), 4.20 (dd, J=9.9; 3.3, 1), 4.07 (m, 2), 3.80 (d, J=3.0, 1), 3.60 (m, 2), 3.34 (m, 2), 2.84 (m, 1), 2.17 (m, 1), 2.10 (s, 3) 2.01 (m, 1), 1.77 (m, 3), 1.40 (m, 4), 0.91 (m, 12); MS (ESPOS): 419 [M+H]$^+$.

## Example 55

### Preparation of 1-(4-n-propylpiperid-6-yl)-N-{ 1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2,2-difluoro-prop-1-yl}acetamide

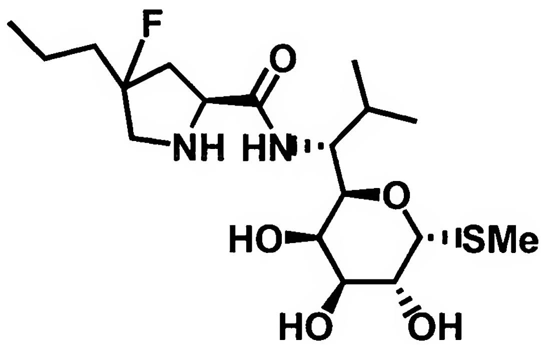


[0555] To acid **10b** ($R^9$ = propyl) prepared by Method P (53 mg, 0.32 mmol) in DMF (3 mL), lincosamide intermediate, compound **5b** ($R^1$ = Me), prepared by Method I (63 mg, 0.16 mmol) and HATU (121 mg, 0.32 mmol), triethylamine (70 mg, 0.48 mmol) was added at 0°C and stirred at room temperature 16 hours. DMF was removed and the residue was taken in ethyl acetate and washed with saturated bicarbonate (30 mL). The product obtained on removal of solvent was purified on silica gel column using 30% ethyl acetate in hexanes (40 mg, 45 %). To the pure product in methanol (5 mL), water (5 mL), acetic acid (5 mL) and platinum dioxide (50 mg, mmol) was added and hydrogenated at 60 psi for 16 hours. After filtering the catalyst, the solvent was removed to obtain the crude product which was taken in methanol (3 mL). Potassium carbonate (125 mg, 0.83 mmol) in water (1 mL) was added to it and stirred 16 hours. Solvents were then removed and the crude product purified on column chromatography using 20 % methanol in dichloromethane. The lower Rf fraction resulted in the title compound (10 mg, 33%).

[0556] $^1H$ NMR (300 MHz, $CD_3OD$) δ 5.28 (d, J = 5.4, 1), 4.73 (s, 1), 4.57-4.65 (m, 1), 4.33-4.42 (m, 1), 4.05 (m, 1), 3.89 (s, 1), 3.53-3.57 (m, 2), 2.83 (t, J = 12.3, 1), 2.09 (s, 3), 1.63-1.84 (m, 5), 1.16-1.37 (m, 6), 0.93 (m, 3). MS(ESPOS): 427 $[M+H]^+$.

## Example 56

### Preparation of 1-[4-n-propyl-4-fluoro-pyrrolidin-2-yl]-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide



[0557] To a stirred solution of (2S, 4R)-4-hydroxyproline (Aldrich) (25 g, 108 mmol) in methanol (50 mL) at 0 °C was added trimethylsilyldiazomethene (24.6 g, 216 mmol). The mixture was stirred at 0 °C for 1 hour. The residue obtained on removal of solvent and purification by column chromatography using 50% ethyl acetate in hexanes (27 g, 100%) was used in the next step. To oxalyl chloride (15 g, 118 mmol) in DCM (15 mL) at -78 °C, DMSO (18.6 mL, 236 mmol) was added slowly over 15 minutes. After the completion of addition, the above product (2S, 4R)-N-Boc-4-hydroxyproline methylester (26.5 g, 108 mmol) in DCM (100 mL) was added at -78 °C for 20 minutes. Triethylamine (54.6 g, 540 mmol) was added followed by stirring at room temperature for 2 hours. The reaction mixture was then washed with 10% aq HCl (200 mL) and the organic layer was separated and dried over sodium sulfate. The crude product obtained on removal of solvent was purified on silica gel column chromatography using 50% EtoAc in hexanes to obtain (2S, 4R)-N-Boc-4-Ketoproline methylester (20 g, 78%).

[0558] $^1$H NMR (300 MHz, $CDCl_3$) δ 4.80 (m, 1), 3.88 (d, J=8.7, 2), 3.77 (s, 3), 2.98 (m, 1), 2.58 (m, 1), 1.45 (s, 9); MS (ESPOS): 244 $[M+H]^+$.

[0559] To a stirred solution of (2S, 4R)-N-Boc-4-Ketoproline methylester (1 g, 4.11 mmol) in THF (10 mL), tetraallyltin (1.08 mL, 4.52 mmol) in dry THF was added, then cooled to 0 °C before borontrifluoride etherate (0.520 mL, 4.11 mmol) was added drop wise. The mixture was stirred at 0 °C for 1h and then at room temperature for an additional 2 hours. Potassium fluoride (360 mg in 5mL water) and celite (1 g) was added and the reaction mixture was stirred for an hour. The reaction mixture was filtered and concentrated to dryness and the residue was dissolved in DCM (200 mL), washed with water (100mL) and brine 100 mL), dried over $MgSO_4$

and evaporated to dryness. T he residue obtained on removal of solvent was purified by silica gel column chromatography using 50% EtOAc in hexanes to obtain 4-Hydroxy-4-allylproline methylester (0.94 g, 80%).

**[0560]** $^1$H NMR (300 MHz, $CDCl_3$) δ 5.87 (m, 1), 5.19 (m, 2), 4.34 (m, 1), 3.75 (d, J=4.8, 3), 3.50 (m, 3), 2.37 (m, 1), 2.21 (m, 1), 1.39 (d, J=12.9, 9); MS (ESPOS): 308 $[M+Na]^+$.

**[0561]** To a stirred solution of DAST (1.06 g, 6.58 mmol) in DCM (10 mL) at -78 °C, 4-hydroxy-4-allylproline methylester (940 mg, 3.3 mmol) in dry DCM (10 mL) was added slowly. The mixture was then stirred at -78 °C for 1h, then at -10 °C for an additional 1h. DCM (50 mL) was added, quenched with $NH_4Cl$ (10%, 150 mL) and the organic layer was separated, dried over sodium sulfate and evaporated to dryness. The residue obtained on removal of solvent was purified by silica gel column chromatography using 5% EtOAc in hexanes as eluent to obtain 4-fluoro-4-allylproline methylester (330 mg, 34%).

**[0562]** $^1$H NMR (300 MHz, $CDCl_{13}$) δ 5.82 (m, 1), 5.12 (m, 2), 4.43 (m, 1), 3.66 (s, 3), 3.47 (m, 1), 2.37 (m, 1), 2.43 (m, 4), 1.37 (dd, J=4.5, 13.8, 9); MS (ESPOS): 310 $[M+Na]^+$.

**[0563]** To a solution of 4-fluoro-4-allylproline methylester (0.33 g, 1.15 mmol) in MeOH (15 mL) was added 10% Pd/C (40 mg) and hydrogenated at 1 atmosphere. The catalyst was filtered through celite and washed with methanol. To the product obtained on removal of solvent (330 mg, 1.15 mmol) in THF (12 mL) was added aq lithium hydroxide monohydrate (60 mg, 1.38 mmol). The reaction mixture was stirred at room temperature overnight. THF was removed and the residue was taken up in ethyl acetate (50 mL), washed with 10% citric acid (100 mL) and brine (20 mL). Removal of solvent resulted in 4-fluoro-4-propylproline (310 mg, 100%).

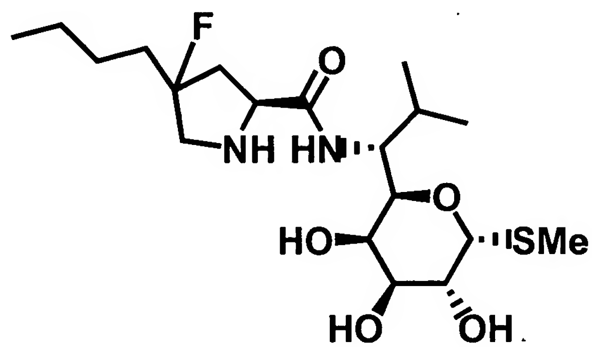
**[0564]** $^1$H NMR (300 MHz, $CD_3OD$) δ 4.43 (m, 1), 3.71 (m, 6), 2.51 (m, 2), 1.98 (m, 3), 1.45 (m, 9), 0.96 (m, 3); MS (ESNEG): 274 $[M-H]^-$.

**[0565]** To a solution of 4-fluoro-4-propylproline (310 mg, 1.15 mmol) in DMF (3 mL) at 0 °C, 7-Methyl MTL **2b** ($R^1$ =Me, $R^2$=Me) (272 mg, 1.15 mmol), HBTU (469 mg, 1.3 mmol) and DIEA (290 mg, 2.3 mmol) was added, left stirred at room temperature for 16 hours. DMF was removed and the residue obtained was purified by 3% MeOH in DCM(40 mg, 93%). The product from the column purification was taken in DCE (6 mL), to which triethylsilane (0.16 mL), TFA (2 mL) and water (0.16 mL) was added and stirred at room temperature for 1.5 hours. Removal of solvent followed by purification on silica gel column chromatography using 10% MeOH in DCM resulted in the title compound as isomeric mixtures with lower RF fraction (160 mg, 50%).

[0566] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.25 (d, J=5.7, 1), 4.46 (m, 1), 4.24 (dd, J=5.7, 10.2, 1), 4.08 (m, 2), 3.81 (d, J=2.4, 1), 3.52 (m, 3), 2.73 (m, 1), 2.10 (m, 4), 1.88 (m, 2), 1.50 (m, 2), 0.99 (t, J=7.5, 3), 0.91 (dd, J=3.0, 6.9, 6); MS (ESPOS): 409 $[M+H]^+$; and higher Rf fraction (40 mg, 12%). $^1$H NMR (300 MHz, $CD_3OD$) δ 5.38 (d, J=5.4, 1), 4.46 (m, 1), 4.24 (dd, J=2.7, 7.2, 1), 4.08 (m, 2), 3.81 (d, J=2.4, 1), 3.64 (m, 3), 2.73 (m, 1), 2.11 (m, 4), 1.84 (m, 2), 1.47 (m, 2), 0.98 (t, J=7.5, 3), 0.91 (dd, J=3.0, 6.9, 6); MS (METHOD ESPOS): 409 $[M+H]^+$.

## Example 57

**Preparation of 1-[4-n-butyl-4-fluoro-pyrrolidin-2-yl]-N-{1-[3,4,5-trihydroxy-6-(methylthio)tetrahydropyran-2-yl]-2-methylprop-1-yl}acetamide**




[0567] To ethyl acetylene (140 mg, 2.6 mmol) in THF (5 mL) at –78 °C, n-butyllithium (1.1 mL, 2.6 mmol) was added with stirring at –78 °C for 1 hour. Then n-(tert-Butoxycarbonyl)-L-proline-4-ketone (described in the example 56) (570 mg, 2.3 mmol) in THF (5 mL) was added at –78 °C with stirring for 2 hours and then let it warm to –40 °C over 1 hour. The reaction mixture was extracted with EtOAc (20 mL), washed with saturated $NH_4Cl$ (5 mL) and dried over sodium sulfate. Purification of the crude product was carried out by silica gel chromatography using 50% EtOAc in hexane to obtain the N-boc-4-butyl-4-hydroxy-prolinemethyl ester (520 mg, 73%). To the DAST (556 mg, 3.4 mmol) in DCM (5 mL) at –78 °C, was added a solution of the above ester (520 mg, 1.7 mmol) in DCM (5 mL) at –78 °C and stirred for 1 hour. The reaction mixture was extracted with DCM (50 mL) and washed with $NaHCO_3$ (30 mL, 10%). The product obtained after removal of solvent was purified by silica gel chromatography using 5% EtOAc in hexanes to obtain N-(tert-butoxycarbonyl)-L-proline-4-fluoro-4-butane (276 mg, 52%).

[0568] $^1$H NMR (300 MHz, $CD_3OD$) δ 4.41 (m, 1), 3.83 (m, 1), 3.71 (s, 3), 3.45 (m, 1), 2.55-1.54 (m, 8), 1.39 (m, 9), 0.89 (m, 3); MS (ESPOS): 326 $[M+Na]^+$.

[0569] To a solution of N-(tert-butoxycarbonyl)-L-proline-4-fluoro-4-butane (270 mg, 0.89 mmol) in THF (12 mL) and water (4 mL), was added lithium hydroxide monohydrate (45 mg, 1.07 mmol). The reaction mixture was stirred at room temperature for 16 hours. THF was removed under vacuum and the residue was taken up in ethyl acetate (150 mL), washed with 10% citric acid (100 mL) and brine (20mL). Removal of solvent resulted in N-(tert-butoxy)-L-proline-4-fluoro-4-butyl-2-carboxylic acid (260 mg, 100%).

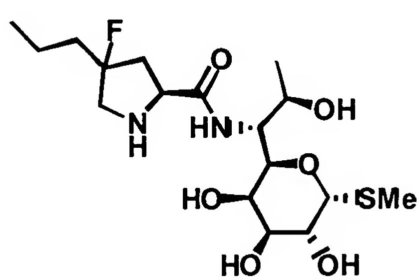
[0570] $^1$H NMR (300 MHz, $CD_3OD$) δ 4.32 (m, 1), 3.72 (m, 2), 2.58 (m, 2), 2.10-1.63 (m, 6), 1.42 (m, 9), 0.93 (t, J=6.6, 3); MS (ESNEG): 288 $[M-H]^-$.

[0571] To a solution of N-(tert-butoxy)-L-proline-4-fluoro-4-butyl-2-carboxylic acid (135 mg, 0.46 mmol) in DMF (3 mL) at 0 °C, 7-Methy MTL **2b** ($R^1$ =Me, $R^2$=Me) (135 mg, 0.46 mmol), HBTU (194 mg, 0.51 mmol), DIEA (120 mg, 0.93 mmol) was added, left it at room temperature for 16 hours. The product obtained after removing DMF and purification by column chromatography using 5% MeOH in DCM (189 mg, 77%) was taken in DCE (6 mL). Triethylsilane (0.16 mL), TFA (2 mL) and water (0.16 mL) was added, stirred at room temperature for 1.5 hours. The residue obtained on removal of solvent was purified by column chromatography using 10% MeOH in DCM to obtain the title compound (156 mg, 96%).

[0572] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.26 (d, J=5.7, 1), 4.55 (m, 1), 4.27 (dd, J=3.3, 10.2, 1), 4.08 (m, 2), 3.82 (d, J=3.0, 1), 3.58 (m, 3), 2.79 (m, 1), 2.22 (m, 1), 2.10 (s, 3), 1.89 (m, 3), 1.40 (m, 4), 0.91 (m, 9); MS (ESPOS): 423 $[M+H]^+$.

## Example 58

**4-Fluoro-4-propyl-pyrrolidine-2-carboxylic acid [2-hydroxy-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**

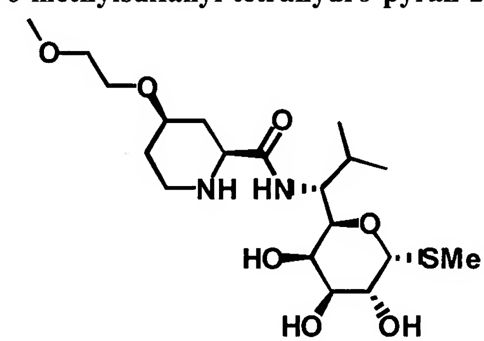


**[0573]** N-(tert-butoxycarbonyl)-4-fluoro-4-propyl-L-proline was prepared as described in the previous example (except using n-propyl lithium in the place of n-butyl lithium) (164 mg, 0.57 mmol) was suspended in dry acetonitrile (4 mL). Triethylamine (332 μL, 3.02 mmol) was added and the reaction mixture was cooled to 0°C. Isobutyl chloroformate (78 μL, 0.57 mmol) was added and after 10 min the reaction was allowed to warm to 4°C. After 1.5 h a solution of MTL (151 mg, 0.57 mmol) in 1:1 acetone: water (4 mL) was added and the reaction mixture was stirred for 10h at rt. The reaction mixture was evaporated to dryness and chromatographed on silica 95:5 dichloromethane/MeOH to 95:8 dichloromethane/MeOH to provide the product as a colorless oil (137 mg, 45%): TLC Rf 0.32 (9:1 dichloromethane/MeOH).

**[0574]** To a solution of the above boc protected lincosamide (125 mg,) in DCM (2.0 mL) was added a solution of DCE (10.0 mL), trifluoroacetic acid (5 mL) methyl sulfide (0.3 mL), and water (0.3 mL). The reaction mixture was stirred at rt for 40 min then diluted with DCE (25.0 mL). The solvent was removed under vacuum and co-evaporated with DCE twice. The residue was purified by chromatography on fluorosil 20% MeOH (0.25M $NH_3$) in DCM to provide the product as a colorless solid (30.0 mg, 30%).

## Example 59

### Preparation of 4-(2-methoxyethoxy)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide




**[0575]** The title compound was made using the synthetic sequence found in Method S starting from 4-hydroxypyridine-2-carboxylic acid, substituting 2-methoxyethyl bromide as the alkylating agent.

**[0576]** Compound **15a** ($R^9$ = 2-methoxyethoxy): $^1H$ NMR (300 MHz, $CD_3OD$) δ 8.40 (d, J=6.0, 1), 7.69 (d, J=2.4, 1), 7.20 (dd, J=2.7, 6.3, 1), 4.35 (m, 2), 3.80 (m, 2), 3.40 (s, 3). MS (ESNEG): 196[M-H]$^-$.

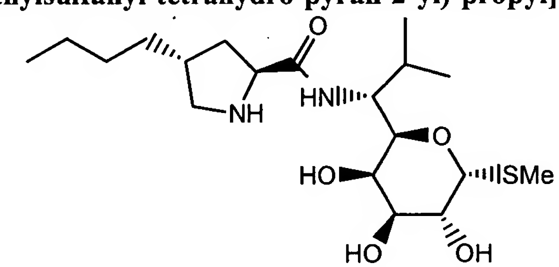
[0577] Compound **15b** ($R^1$=Me, $R^2$=Me, $R^9$= 2-methoxyethoxy): $^1$H NMR (300 MHz, $CD_3OD$) δ 8.43 (d, J=5.7, 1), 7.65 (d, J=2.4, 1), 7.12 (dd, J=2.4, 5.7, 1), 5.27 (d, J=5.4, 1), 4.10-4.87 (m, 4), 3.85 (d, J=3.3, 1), 3.77 (m, 2), 3.55 (m, 1), 3.41 (s, 3), 2.26 (m, 1), 2.11 (s, 1), 0.998 (m, 6). MS (ESPOS): 431 $[M+H]^+$.

[0578] Title compound (10 mg, 10%). $^1$H NMR (300 MHz, $D_2O$) δ 5.18 (d, J=6.0, 1), 4.00 (m, 3), 3.70 (m, 1), 3.56 (m, 1), 3.45 (m, 3), 3.26 (m, 1), 3.16 (m, 3), 3.10 (m, 1), 2.80 (m, 1), 2.48 (m, 1), 2.22 (m, 1), 1.96 (m, 4), 1.17-1.72 (m, 4), 0.70 (m, 6); MS (ESPOS): 437 $[M+H]^+$.

## Examples 60-62

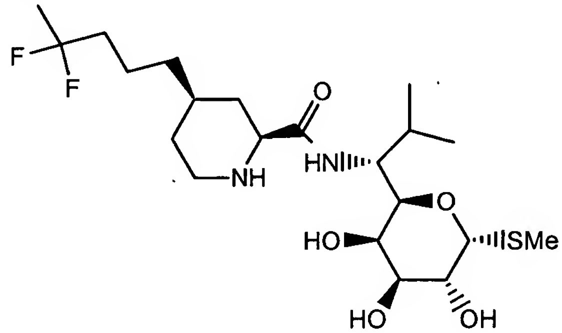
### Example 60

**Preparation of 4-Butyl-pyrrolidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



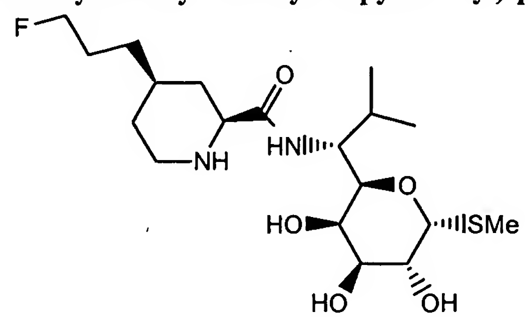
### Example 61

**Preparation of 4-(4,4-Difluoro-pentyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



## Example 62

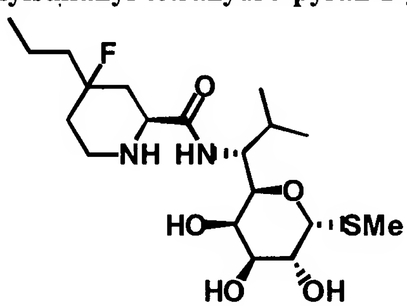
**Preparation of 4-(3-Fluoro-propyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



**[0579]** Examples 60 to 62 were prepared using methods and techniques describe herein utilizing commercially available starting materials where appropriate.

## Example 63

**Preparation of 4-Fluoro-4-propyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**

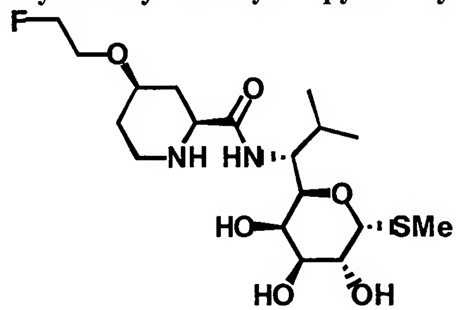


**[0580]** Lincosamine **2b** ($R^1$=Me, $R^2$=Me) was coupled to carbamate **21d** ($P_2$=Boc, m = 2, $R^9$ = *n*-propyl) as depicted in general coupling scheme 11 to provide intermediate **11a** ($R^1$=$R^2$ =Me, $R^3$=H, $R^9$=propyl/fluoro, $P^1$=H, $P_2$=carboxylic acid-*t*-butyl ester, m=2) which was deprotected under acidic conditions to provide the title compound.

**[0581]** HPLC: $C_{18}$ 3.5 µm, 4.6 × 30 mm Column; gradient eluent 2%–98% MeCN over 10 min; 1.5 mL/min): $R_t$ = 3.696 min); $^1$H NMR (300 MHz, $CD_3OD$) δ 5.36 (d, *J*= 5.8, 1), 4.24 (dd, *J* = 3.3, 12.9, 1), 4.20 (s, 2), 4.12 (dd, *J* = 6.0, 10.4, 1), 3.88 (d, *J* = 3.3, 1), 3.65 (dd, *J* = 3.0, 10.4, 1), 3.48 (dd, *J* = 4.1, 13.1, 1), 3.33 (ddd, *J* = 3.6, 3.6, 13.5, 1), 2.43-2.45 (m, 1), 2.22-1.58 (m, 6), 2.16 (s, 3), 1.48 (m, 2), 0.94 (t, *J* = 7.1, 3), 0.88 (d, *J*= 6.9, 6); $^{19}$F NMR ($CD_3OD$) δ-158.8-δ-159.0 (sextuplet), MS (ESPOS): 423.2.

## Example 64

**Preparation of 4-(2-Fluoroethoxy)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



[0582] The title compound was made using the synthetic sequence found in general method S starting from 4-hydroxypyridine-2-carboxylic acid **10b** ($R^9$ = hydroxy) substituting 2-fluoroethyl bromide as the alkylating agent.

[0583] **15a** ($R^{9'}$=2-fluoroethoxy): $^1$H NMR (300 MHz, $CD_3OD$) δ 8.40 (d, *J*=6.0, 1), 7.73 (d, *J*=2.7, 1), 7.24 (dd, *J*=2.4, 6.0, 1), 4.87 (m, 2), 4.50 (m, 2). MS (ESNEG): 184 $[M-H]^-$.

[0584] **15b** ($R^1$=$R^2$ =Me, $R^3$=H, $R^{9'}$=2-fluoroethoxy): $^1$H NMR (300 MHz, $CD_3OD$) δ 8.45 (d, *J*=5.7, 1), 7.67 (d, *J*=2.4, 1), 7.14 (dd, *J*=2.7, 5.7, 1), 5.27 (d, *J*=5.7, 1), 4.68 (m, 1), 4.43 (m, 1), 4.12-4.33 (m, 3), 4.10 (dd, *J*=6.0, 10.2, 1), 3.18-3.84 (m, 3), 2.26 (m, 1), 2.11 (s, 3), 1.00 (t, *J*=5.1, 6). MS (ESPOS): 419 $[M + H]^+$.

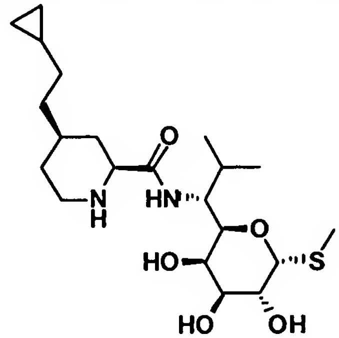
[0585] Title compound (20 mg, 14%): $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, *J*=5.7, 1), 4.59 (t, *J*=4.2, 1), 4.43 (t, *J*=4.2, 1), 4.18 (dd, *J*=3.3, 6.6, 1), 4.07 (m, 2), 3.80 (m, 2), 3.73 (m, 1), 3.55 (m, 2), 3.48 (m, 1), 3.21 (m, 1), 2.74 (m, 1), 2.32 (m, 1), 2.18 (m, 1), 2.10 (s, 3) 1.38 (m, 3), 0.93 (m, 6); MS (ESPOS): 425 $[M + H]^+$.

## Example 65

[0586] There is no Example 65.

## Example 66

**Preparation of 4-(2-Cyclopropyl-ethyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



[0587] Compound **14c** ($R^9$=2-cyclopropylethyl) was prepared using the methods described in general method R.

[0588] To a stirred suspension of **14a** (0.5 g, 1.9 mmol, 1 equiv), triphenylphosphine (39.9 mg, 0.15 mmol, 0.08 equiv), copper (I) iodide (28.9 mg, 0.15 mmol, 0.08 equiv), palladium acetate (17 mg, 0.076 mmol, 0.04 equiv) in triethylamine (7 mL) under dry nitrogen, was added cyclopropyl acetylene (Aldrich) (0.25 g, 3.8 mmol, 2 equiv). The mixture was stirred at rt overnight. The solvent was removed under vacuum to give a dark residue. The residue was purified by column chromatography to give **14b** ($R^{9'}$=2-cyclopropyl-eth-1-ynyl) (0.39 g, 100%) as a yellow oil.

[0589] $^1$H NMR (300 MHz, $CDCl_3$) δ 8.65-8.56 (m, 1), 8.06-7.99 (m, 1), 7.40-7.32 (m, 1), 3.98 (s, 3), 1.50-1.40 (m, 1), 0.96-0.81 (m, 4). MS (ESPOS): 202.0 $[M+H]^+$.

[0590] To a solution of **14b** ($R^{9'}$=2-cyclopropyl-eth-1-ynyl) (0.39 g, 1.9 mmol) in methanol (15 mL) was added 10% palladium on carbon (0.2 g). The mixture was purged and charged with hydrogen (1 atm) and stirred at rt overnight. The palladium was removed by filtration and the filtrate was concentrated to give **14c** ($R^9$=2-cyclopropylethyl) (0.38 g, 97%) as a yellow oil.

[0591] $^1$H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, $J$=4.5, 1), 8.00-7.96 (m, 1), 7.34-7.29 (m, 1), 3.99 (s, 3), 2.78 (t, $J$=7.6, 2), 1.58-1.49 (m, 2), 0.71-0.59 (m, 1), 0.47-0.38 (m, 2), 0.06-0.02 (m, 2); MS (ESPOS): 228.2 $[M + Na]^+$.

[0592] To a mixture of **14c** ($R^9$=2-cyclopropylethyl) (0.38 g) in MeOH (8 mL) and water (8 mL) were added conc. HCl (158 μL) and platinum oxide (0.2 g). The mixture was purged and charged with hydrogen (1 atm) and stirred overnight. The platinum oxide was removed by filtration and the filtrate was evaporated to give a light yellow solid.

[0593] To the above residue was added 2N NaOH (3.8 mL) and *t*-butylalcohol (2 mL). The reaction mixture was stirred at rt for 2 h, di-*t*-butyl dicarbonate (0.62 g, 2.85 mmol) was then added and the mixture stirred overnight. The solvent was removed under vacuum and the resulting residue was diluted with water, then washed with ether. The aqueous layer was acidified with 2N HCl to pH=2.0, and extracted with ethyl acetate (2 x). The combined organic layers were dried and concentrated to give 4-(2-cyclopropylethyl)-piperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (0.42 g, 77 %) as a clear syrup.

[0594] MS (ESPOS): 320.3 $[M + Na]^+$. MS (ESNEG): 296.2 $[M-H]^-$.

[0595] To a solution of 4-(2-cyclopropylethyl)-piperidine-1,2-dicarboxylic acid-1-*tert*-butyl ester (115 mg, 0.387 mmol, 1 equiv) and **2b** ($R^1$=Me, $R^2$=Me) HCl salt (111.4 mg, 0.387 mmol, 1 equiv) in DMF (2.4 mL) at r.t. was added DIEA (100 μL, 0.774 mmol, 2 equiv), followed by HBTU (162 mg, 0.426 mmol, 1.1 equiv). The reaction mixture was stirred at rt for 3 hrs then evaporated under high vacuum to dryness. The residue was diluted with ethyl acetate, washed with 1:1 10% citric acid/brine (1 x), sat. aqueous sodium bicarbonate (1 x), brine (1 x), dried and concentrated. The residue was purified by chromatography to give the desired 1'-Boc protected lincosamide product **11a** ($R^1$=$R^2$ =Me, $R^3$=H, $R^9$=2-cyclopropylethyl, $P^1$=H, $P^2$=carboxylic acid-*t*-butyl ester) (126 mg, 61%) as a clear syrup.

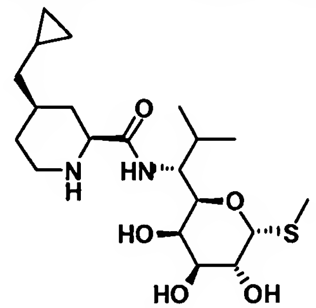
[0596] MS (ESPOS): 531.3 $[M+H]^+$.

[0597] To a solution of the above **11a** ($R^1$=$R^2$ =Me, $R^3$=H, $R^9$=2-cyclopropylethyl, $P^1$=H, $P^2$=carboxylic acid-*t*-butyl ester, m=2) in DCE (12 mL) at 0 °C was added a solution of trifluoroacetic acid (3 mL) and water (0.375 mL). The reaction mixture was stirred at 0 °C for 5 min and at rt for 35 min. The reaction solvent was removed under vacuum and co-evaporated with toluene twice, and the resulting residue was purified by semi-preparative HPLC (Waters Nova-Pak® HR $C_{18}$, 6 μm particle size, 60 Å pore size, 20 mm ID × 100 mm, 5–60% acetonitrile in $H_2O$ w/ 0.1% AcOH over 30 min, 20 mL/min flow rate) to provide the title compound of example 66 (25 mg, 27 %) as a white solid.

[0598] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, *J*=6, 1), 4.19 (dd, *J*=3.4, 10, 1), 4.10-4.04 (m, 2), 3.81-3.72 (m, 2), 3.51 (dd, *J*=3.3, 10.2, 1), 3.42-3.33 (m, 1), 3.02-2.90 (m, 1), 2.20-2.12 (m, 1), 2.11 (s, 3), 1.94-1.86 (m, 1), 1.76-1.64 (m, 1), 1.48-1.20 (m, 7), 0.94-0.85 (m, 6), 0.73-0.62 (m, 1), 0.47-0.38 (m, 2), 0.05-0.02 (m, 2). MS (ESPOS): 431.3 $[M+H]^+$.

## Example 67

### Preparation of 4-Cyclopropylmethyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide



[0599] 4-Cyclopropylmethylpyridine-2-carboxylic acid, compound **10b** ($R^9$=cyclopropylmethyl), was made by employing Method P using the starting material 4-Cyclopropylmethylpyridine prepared as described by Osuch et al, *Journal of the American Chemical Society*, **1955**, *78*, 1723.

[0600] To a -78 °C solution of 4-picoline (1.1 g, 11.8 mmol) in THF (5 mL) was added a solution of LDA 2M in THF/heptane/ethylbenzene (Aldrich) (5.9 mL, 11.8 mmol). The resulting reaction mixture was stirred at -78 °C for 3 h then -40 °C for 1 h. Cyclopropyl bromide (1.43 g, 11.8 mmol) was added at -78 °C, the reaction mixture was alloed to warm up to room temperature and was stirred at room temperature for 1 h. To the reaction mixture was added saturated aqueous $NH_4Cl$ (10 mL), the aqueous phase was extracted with EtOAc (10 x 2 mL), and the combined organic extracts dried over $Na_2SO_4$. 4-Cyclopropylmethylpyridine-2-carboxylic acid (0.5 g, 31%) was obtained after the solvent was removed and used without further purification.

[0601] To a 0°C solution of 4-Cyclopropylmethylpyridine-2-carboxylic acid **(10b)** ($R^9$=cyclopropylmethyl) (147 mg, 0.83 mmol), **2b** ($R^1$=Me, $R^2$=Me) HCl salt (238 mg, 0.83 mmol) and TEA (231 μL, 1.66 mmol) in DMF (2 mL) was added solid HBTU (346 mg, 0.91 mmol), and the resulting reaction mixture was stirred overnight. Reaction solvents were removed, and the residue purified by silica gel column chromatography at 50-100% EtOAc/Hexane to provide the desired lincosamide product **11b** ($R^1$=$R^2$ =Me, $R^3$=H, $R^9$=cyclopropylmethyl, $P^1$=H) (260 mg, 76%).

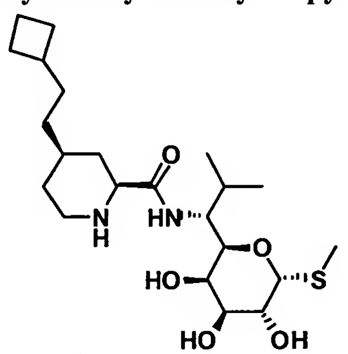
[0602] To a solution of **11b** ($R^1$=$R^2$ =Me, $R^3$=H, $R^9$=cyclopropylmethyl, $P^1$=H) (250 mg, 0.6 mmol) in water (10 mL), AcOH (2 mL), MeOH (3 mL) was added $PtO_2$ (200 mg), and the

reaction mixture was hydrogenated at 50 psi for 5 hr. The solvent was removed to obtain the crude lincosamide product. Purification was carried by silica gel column chromatography (20% MeOH/DCM), then HPLC (Waters Nova-Pak® HR $C_{18}$, 6 µm particle size, 60 Å pore size, 20 mm ID × 100 mm, 5–60% acetonitrile in $H_2O$ w/ 0.1% AcOH over 30 min, 20 mL/min flow rate) to provide the title compound (13 mg, 5%) as a colorless solid.

**[0603]** $^1$H NMR (300 MHz, $CD_3OD$) δ 5.23 (d, *J*=6, 1), 4.26-4.10 (m, 3), 3.83-3.78 (m, 2), 3.55-3.33 (m, 2), 3.07-2.95 (m, 1), 2.34-2.17 (m, 2), 2.12 (s, 3), 2.00-1.80 (m, 4), 1.42-1.15 (m, 4), 1.00-0.90 (m, 6), 0.79-0.66 (m, 1), 0.53-0.45 (m, 2), 0.12-0.04 (m, 2); MS (ESPOS): 417.3 $[M+H]^+$.

## Example 68

### Preparation of 4-(2-Cyclobutyl-ethyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide



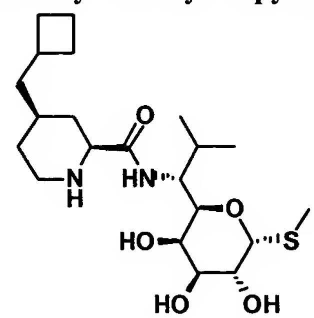

**[0604]** 4-(2-Cyclobutyl-ethyl)-pyridine-2-carboxylic acid, compound **10b** ($R^9$=2-cyclobutyl-ethyl), was made by employing Method P using the starting material 4-(2-Cyclobutyl-ethyl)-pyridine prepared as described by Osuch et al, *Journal of the American Chemical Society*, **1955**, *78*, 1723.

**[0605]** Lincosamine **2b** ($R^1$=Me, $R^2$=Me) was coupled to 4-(2-cyclobutyl-ethyl)-pyridine-2-carboxylic acid **10b** ($R^9$=cyclobutyl-ethyl) as depicted in general coupling scheme 11 to provide intermediate **11b** ($R^1$=$R^2$ =Me, $R^3$=H, $R^9$= 2-cyclobutyl-ethyl, $P^1$=H) which was reduced by catalytic hydrogenation to the title compound.

**[0606]** MS (ESPOS): 445.2 $[M+H]^+$.

## Example 69

**Preparation of 4-Cyclobutylmethyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



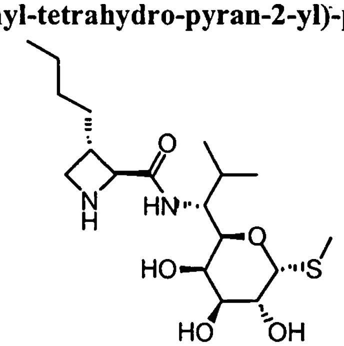
[0607] 4-Cyclobutylmethylpyridine-2-carboxylic acid, compound **(10b)** ($R^9$=4-cyclobutylmethyl) was made by employing Method P using the starting material 4-cyclobutylmethylpyridine prepared as described by Osuch et al, *Journal of the American Chemical Society*, **1955**, *78*, 1723.

[0608] Lincosamine **2b** ($R^1$=Me, $R^2$=Me) was coupled to 4-cyclobutylmethylpyridine-2-carboxylic acid, compound **10b** ($R^9$=4-cyclobutylmethyl), as depicted in general coupling scheme 11 to provide intermediate **11b** ($R^1$=$R^2$ =Me, $R^3$=H, $R^9$= cyclobutyl-methyl, $P^1$=H), which was reduced by catalytic hydrogenation to the title compound.

[0609] MS (ESPOS): 431.3 $[M+H]^+$.

## Example 70

**Preparation of 3-Butyl-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



[0610] To a solution of azetedine acid **16f** ($R^9$=butyl) (52 mg, 0.20 mmol, 1 equiv), aminosugar (58 mg, 0.20 mmol, 1 equiv) and HBTU (84 mg, 0.22 mmol, 1.1 equiv) in DMF (2.0 mL) at 23 °C was added DIPEA (88 µL, 0.51 mmol, 2.5 equiv). After stirring for 12 h at 23

°C, DMF was removed in vacuo, then the residue was partitioned between EtOAc (100 mL) and 1:1 brine: 10% aqueous citric acid (100 mL). The organic layer was separated and washed with 1:1 brine/saturated aqueous $NaHCO_3$ (100 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated to furnish 82 mg (0.17 mmol, 84%) **11a** ($R^1$=$R^2$ =Me, $R^3$=H, $R^9$=butyl, $P^1$=H, $P^2$=carboxylic acid-*t*-butyl ester, m=0) as a glassy solid.

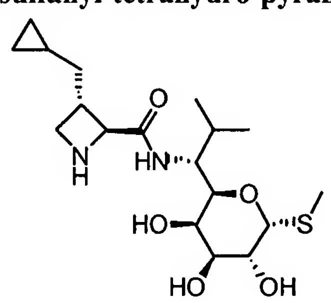
**[0611]** MS (ESPOS): $[M+H]^+$.

**[0612]** To a solution of carbamate **11a** ($R^1$=$R^2$ =Me, $R^3$=H, $R^9$=butyl, $P^1$=H, $P^2$=carboxylic acid-*t*-butyl ester, m=0) (82 mg, 0.17 mmol, 1 equiv) in 1,2-dichloroethane (10 mL) at 23 °C was added $H_2O$ (0.40 mL) followed by TFA (4.0 mL). After stirring for 20 min at 23 °C, toluene (50 mL) was added and the resulting solution was concentrated to dryness. The residue was purified by semi-preparative HPLC (Waters Nova-Pak® HR $C_{18}$, 6 μm particle size, 60 Å pore size, 20 mm ID × 100 mm, 5–60% acetonitrile in $H_2O$ w/ 0.1% HCl over 30 min, 20 mL/min flow rate) to give 41 mg of title compound as a white solid.

**[0613]** $^1$H NMR (300 MHz, $CD_3OD$) δ 5.25 (d, *J*=5.7, 1), 4.60 (d, *J*=7.2, 1), 4.25 (dd, *J*=3.3, 9.9, 1), 4.16–4.05 (m, 2), 3.99 (t, *J*=9.0, 1), 3.81 (d, *J*=3.0, 1), 3.74 (dd, *J*=8.4, 9.9, 1), 3.50 (dd, *J*=3.3, 10.2, 1), 2.90–2.74 (m, 1), 2.23–2.10 (m, 1), 2.10 (s, 3), 1.90–1.67 (m, 2), 1.44–1.24 (m, 4), 1.00–0.86 (m, 9 H). MS (ESPOS): 391.4 $[M+H]^+$.

### Example 71

**Preparation of 3-Cyclopropylmethyl-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**

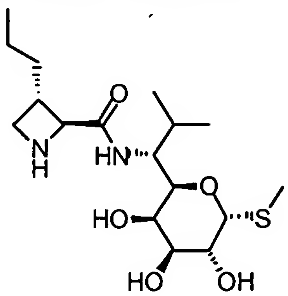



**[0614]** Lincosamine **2b** ($R^1$=Me, $R^2$=Me) was coupled to azetedine acid **16f** ($R^9$=cyclopropylmethyl) as depicted in general coupling scheme 11 to provide intermediate **11a** ($R^1$=$R^2$ =Me, $R^3$=H, $R^9$=cyclopropylmethyl, $P^1$=H, $P^2$=carboxylic acid-*t*-butyl ester, m=0) which was deprotected under acidic conditions to provide the title compound.

[0615] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.25 (d, *J*=5.7, 1), 4.65 (d, *J*=7.5, 1), 4.25 (dd, *J*=3.9, 9.6, 1), 4.13–3.99 (m, 3), 3.86–3.79 (m, 2), 3.51 (dd, *J*=3.3, 10.2, 1), 3.00–2.87 (m, 1), 2.21–2.09 (m, 1), 2.11 (s, 3), 1.83–1.72 (m, 1), 1.62–1.51 (m, 1), 0.94 (d, *J*=6.9, 3), 0.89 (d, *J*=6.9, 3), 0.82–0.70 (m, 1), 0.58–0.47 (m, 2), 0.18–0.08 (m, 2 H). MS (ESPOS): 389.2 $[M+H]^+$.

## Example 72

### Preparation of 3-Propyl-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide

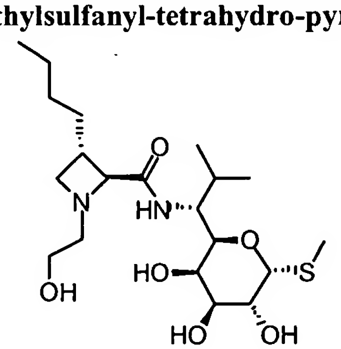


[0616] Lincosamine **2b** ($R^1$=Me, $R^2$=Me) was coupled to azetedine acid **16f** ($R^9$=propyl) as depicted in general coupling scheme 11 to provide intermediate **11a** $R^1$=$R^2$ =Me, $R^3$=H, $R^9$=propyl, $P^1$=H, $P^2$=carboxylic acid-*t*-butyl ester, m=0) which was deprotected under acidic conditions to provide the title compound.

[0617] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.26 (d, *J*=5.4, 1), 4.60 (d, *J*=7.5, 1), 4.26 (dd, *J*=3.3, 9.6, 1), 4.13–3.99 (m, 3), 3.81 (d, *J*=3.3, 1), 3.76 (dd, *J*=5.1, 10.2, 1), 3.51 (dd, *J*=3.3, 9.9, 1), 2.93–2.76 (m, 1), 2.24–2.09 (m, 1), 2.11 (s, 3), 1.84–1.67 (m, 2), 1.48–1.30 (m, 2), 1.01–0.87 (m, 9 H). MS (ESPOS): 377.0 $[M+H]^+$.

## Example 73

### Preparation of 3-Butyl-1-(2-hydroxy-ethyl)-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide

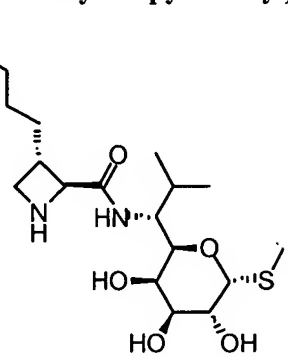


**[0618]** A sample of 3-Butyl-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide prepared in example 70 was alkylated with ethyleneoxide as depicted in scheme 12 ($R^6$=2-hydroxyethyl) to provide the title compound.

**[0619]** $^1$H NMR (300 MHz, $CD_3OD$) δ 5.25 (d, *J*=5.4, 1), 4.13–4.05 (m, 3), 3.83–3.77 (m, 2), 3.64 (t, *J*=9.9, 1), 3.58–3.48 (m, 2), 3.37–3.30 (m, 1), 2.78–2.55 (m, 2), 2.44–2.34 (m, 1), 2.25–2.10 (m, 2), 2.11 (s, 3), 1.80–1.40 (m, 2), 1.39–1.20 (m, 4), 0.95–0.84 (m, 9 H). MS (ESPOS): 435.1 $[M+H]^+$.

## Example 74

### Preparation of 3-Pentyl-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide

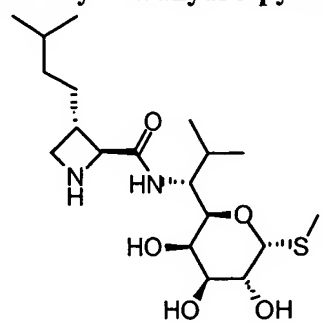



**[0620]** Lincosamine **2b** ($R^1$=Me, $R^2$=Me) was coupled to azetedine acid **16f** ($R^9$=pentyl) as depicted in general coupling scheme 11 to provide intermediate **11a** ($R^1$=$R^2$ =Me, $R^3$=H, $R^9$=pentyl, $P^1$=H, $P^2$=carboxylic acid-*t*-butyl ester, m=0) which was deprotected under acidic conditions to provide the title compound.

**[0621]** $^1$H NMR (300 MHz, $CD_3OD$) δ 5.25 (d, *J*=5.7, 1), 4.55 (d, *J*=6.9, 1), 4.25 (dd, *J*=3.3, 9.9, 1), 4.13–4.04 (m, 2), 4.00 (t, *J*=9.3, 1), 3.80 (d, *J*=3.0, 1), 3.73 (dd, *J*=7.8, 9.9, 1), 3.51 (dd, *J*=3.3, 10.5, 1), 2.88–2.75 (m, 1), 2.23–2.10 (m, 1), 2.11 (s, 3), 1.84–1.60 (m, 2), 1.44–1.26 (m, 6), 0.97–0.86 (m, 9 H). MS (ESPOS): 405.4 $[M+H]^+$.

## Example 75

### Preparation of 3-(3-Methyl-butyl)-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide

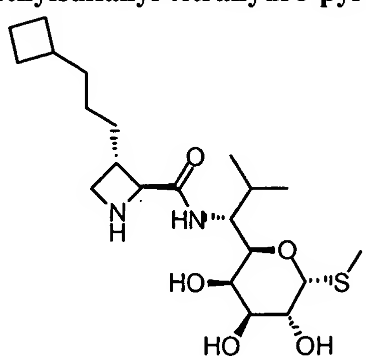


[0622] Lincosamine **2b** ($R^1$=Me, $R^2$=Me) was coupled to azetedine acid **16f** ($R^9$=3-methyl-butyl) as depicted in general coupling scheme 11 to provide intermediate **11a** ($R^1$=$R^2$ =Me, $R^3$=H, $R^9$=3-methyl-butyl, $P^1$=H, $P^2$=carboxylic acid-*t*-butyl ester, m=0) which was deprotected under acidic conditions to provide the title compound.

[0623] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.25 (d, *J*=6.0, 1), 4.55 (d, *J*=7.5, 1), 4.26 (dd, *J*=3.6, 10.2, 1), 4.13–4.04 (m, 2), 4.00 (t, *J*=9.3, 1), 3.80 (d, *J*=3.3, 1), 3.73 (dd, *J*=8.1, 10.2, 1), 3.51 (dd, *J*=3.3, 10.2, 1), 2.87–2.72 (m, 1), 2.24–2.10 (m, 1), 2.11 (s, 3), 1.84–1.70 (m, 2), 1.66–1.50 (m, 1), 1.26–1.10 (m, 2), 0.97–0.86 (m, 12 H). MS (ESPOS): 405.0 $[M+H]^+$.

## Example 76

### Preparation of 3-(3-Cyclobutyl-propyl)-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide

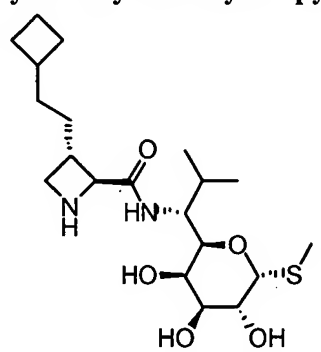


[0624] Lincosamine **2b** ($R^1$=Me, $R^2$=Me) was coupled to azetedine acid **16f** ($R^9$=3-cyclobutyl-propyl) as depicted in general coupling scheme 11 to provide intermediate **11a** ($R^1$=$R^2$ =Me, $R^3$=H, $R^9$=(3-cyclobutyl-propyl), $P^1$=H, $P^2$=carboxylic acid-*t*-butyl ester, m=0) which was deprotected under acidic conditions to provide the title compound.

[0625] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, $J$=5.7, 1), 4.24–4.14 (m, 2), 4.11–4.04 (m, 2), 3.78 (d, $J$=3.3, 1), 3.71 (t, $J$=9.0, 1), 3.54–3.43 (m, 1), 2.76–2.60 (m, 1), 2.34–2.10 (m, 2), 2.10 (s, 3), 2.09–1.97 (m, 2), 1.90–1.51 (m, 7), 1.44–1.11 (m, 3), 0.90 (d, $J$=2.1, 3), 0.88 (d, $J$=2.1, 3 H). MS (ESPOS): 431.3 $[M+H]^+$.

## Example 77

### Preparation of 3-(2-Cyclobutyl-ethyl)-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide

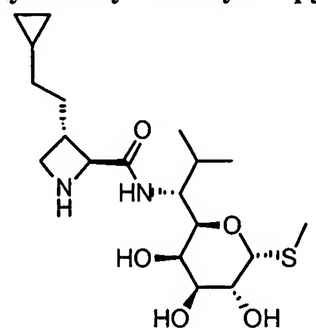



[0626] Lincosamine **2b** ($R^1$=Me, $R^2$=Me) was coupled to azetedine acid **16f** ($R^9$=2-cyclobutyl-ethyl) as depicted in general coupling scheme 11 to provide intermediate **11a** ($R^1$=$R^2$=Me, $R^3$=H, $R^9$=2-cyclobutyl-ethyl, $P^1$=H, $P^2$=carboxylic acid-*t*-butyl ester, m=0) which was deprotected under acidic conditions to provide the title compound.

[0627] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, $J$=6.0, 1), 4.51 (d, $J$=10.2, 1), 4.25 (dd, $J$=3.3, 9.9, 1), 4.12–4.03 (m, 2), 3.96 (t, $J$=9.3, 1), 3.79 (d, $J$=3.0, 1), 3.69 (dd, $J$=8.1, 10.2, 1), 3.50 (dd, $J$=3.3, 10.2, 1), 2.85–2.69 (m, 1), 2.36–2.10 (m, 2), 2.10 (s, 3), 2.09–2.00 (m, 2), 1.95–1.33 (m, 10), 0.92 (d, $J$=6.9, 3), 0.89 (d, $J$=6.9, 3 H). MS (ESPOS): 417.3 $[M+H]^+$.

## Example 78

**Preparation of 3-(2-Cyclopropyl-ethyl)-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**

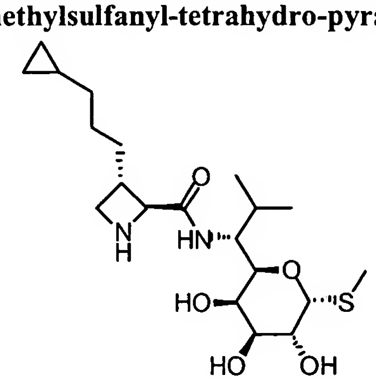


[0628] Lincosamine **2b** ($R^1$=Me, $R^2$=Me) was coupled to azetedine acid **16f** ($R^9$=2-cyclopropyl-ethyl) as depicted in general coupling scheme 11 to provide intermediate **11a** ($R^1$=$R^2$ =Me, $R^3$=H, $R^9$=2-cyclopropyl-ethyl, $P^1$=H, $P^2$=carboxylic acid-*t*-butyl ester, m=0) which was deprotected under acidic conditions to provide the title compound.

[0629] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, *J*=5.7, 1), 4.53 (d, *J*=7.2, 1), 4.24 (dd, *J*=3.3, 9.9, 1), 4.11–4.03 (m, 2), 3.98 (t, *J*=9.6, 1), 3.79 (d, *J*=3.0, 1), 3.73 (dd, *J*=8.1, 9.9, 1), 3.50 (dd, *J*=3.3, 10.2, 1), 2.92–2.77 (m, 1), 2.22–2.09 (m, 1), 2.10 (s, 3), 1.95–1.77 (m, 2), 1.33–1.18 (m, 2), 0.91 (d, *J*=6.9, 3), 0.88 (d, *J*=6.9, 3), 0.73–0.60 (m, 1), 0.48–0.40 (m, 2), 0.08–0.01 (m, 2 H). MS (ESPOS): 403.3 $[M+H]^+$.

## Example 79

**Preparation of 3-(3-Cyclopropyl-propyl)-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



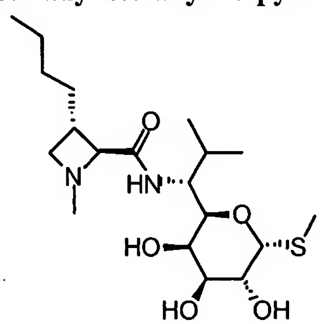
[0630] Lincosamine **2b** ($R^1$=Me, $R^2$=Me) was coupled to azetedine acid **16f** ($R^9$=3-cyclopropyl-propyl) as depicted in general coupling scheme 11 to provide intermediate **11a**

($R^1$=$R^2$ =Me, $R^3$=H, $R^9$=3-cyclopropyl-propyl, $P^1$=H, $P^2$=carboxylic acid-*t*-butyl ester, m=0) which was deprotected under acidic conditions to provide the title compound.

**[0631]** $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, *J*=5.7, 1), 4.54 (d, *J*=7.5, 1), 4.24 (dd, *J*=3.3, 9.9, 1), 4.11–4.03 (m, 2), 3.97 (t, *J*=9.6, 1), 3.79 (d, *J*=3.0, 1), 3.71 (dd, *J*=7.8, 9.9, 1), 3.50 (dd, *J*=3.0, 10.2, 1), 2.88–2.74 (m, 1), 2.23–2.09 (m, 1), 2.10 (s, 3), 1.90–1.68 (m, 2), 1.57–1.33 (m, 2), 1.23 (q, *J*=6.9, 2), 0.91 (d, *J*=6.9, 3), 0.89 (d, *J*=6.9, 3), 0.75–0.60 (m, 1), 0.45–0.38 (m, 2), 0.04–‾0.02 (m, 2 H). MS (ESPOS): 417.3 $[M+H]^+$.

## Example 80

### Preparation of 3-Butyl-1-methyl-azetidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide

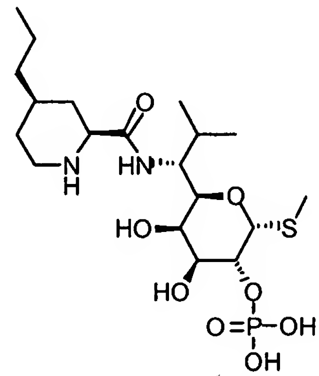



**[0632]** Azetedine acid **16f** ($R^9$ =butyl) was deprotected and N-methylated by treatment with formic acid and formaldehyde under conditions known to persons skilled in the art to provide 3-butyl-1-methyl-azetidine-2-carboxylic acid. Lincosamine **2b** ($R^1$=Me, $R^2$=Me) was coupled to 3-butyl-1-methyl-azetidine-2-carboxylic acid as depicted in general coupling scheme 11 to provide the title compound.

**[0633]** $^1$H NMR (300 MHz, $D_2O$) δ 5.36 (d, *J*=6.0, 1), 4.67 (d, *J*=8.7, 1), 4.31 (t, *J*=9.3, 1), 4.22 (s, 2), 4.10 (dd, *J*=6.0, 10.5, 1), 3.86 (d, *J*=3.3, 1), 3.79 (t, *J*=9.6, 1), 3.64 (dd, *J*=3.3, 10.2, 1), 3.04–2.84 (m, 1), 2.93 (s, 3), 2.25–2.05 (m, 1), 2.14 (s, 3), 1.87–1.68 (m, 2), 1.40–1.20 (m, 4), 0.87 (t, *J*=7.5, 9 H). MS (ESPOS): 405.4 $[M+H]^+$.

## Example 81

### Preparation of Phosphoric acid mono-(4,5-dihydroxy-6-{2-methyl-1-[(4-propyl-piperidine-2-carbonyl)-amino]-propyl}-2-methylsulfanyl-tetrahydro-pyran-3-yl) ester

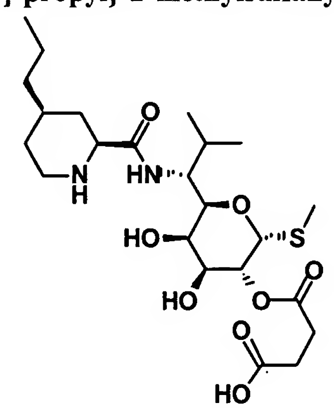


[0634] Synthesis of the title compound, **5** (wherein $R^1$=$R^2$ =Me, $R^3$=H, $R^9$=4-*cis*-n-propyl, $R^{11}$=$PO(OH)_2$) is detailed in Method V.

[0635] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.41 (d, *J*=5.7, 1), 4.53–4.43 (m, 1), 4.10–3.88 (m, 4), 3.73 (dd, *J*=3.0, 9.6, 1), 3.44–3.30 (m, 2), 2.25–2.10 (m, 2), 2.11 (s, 3), 2.00–1.88 (m, 1), 1.86–1.70 (m, 1), 1.44–1.25 (m, 6), 0.98–0.88 (m, 9). MS (ESPOS): 485.1 $[M+H]^+$. MS (ESNEG): 483.0 $[M-H]^-$.

## Example 82

### Preparation of Succinic acid mono-(4,5-dihydroxy-6-{2-methyl-1-[(4-propyl-piperidine-2-carbonyl)-amino]-propyl}-2-methylsulfanyl-tetrahydro-pyran-3-yl) ester



[0636] To a suspension of alcohol **18b** (wherein $R^1$=$R^2$ =Me, $R^3$=H, $R^9$=4-*cis*-n-propyl, m=2) (721 mg, 1.16 mmol, 1 equiv), succinic anhydride (174 mg, 1.74 mmol, 1.5 equiv) and DMAP (71 mg, 0.58 mmol, 0.5 equiv) in 1,2-dichloroethane (3.0 mL) at 23 °C was added $Et_3N$

(0.34 mL, 2.43 mmol, 2.1 equiv). After stirring for 2 h at 23 °C, the reaction mixture was partitioned between EtOAc (100 mL) and 10% aqueous citric acid (100 mL). The organic layer was separated, washed with brine (50 mL), dried ($MgSO_4$) filtered and concentrated to furnish 840 mg of the desired product **18c** (wherein $R^1$=$R^2$ =Me, $R^3$=H, $R^9$=4-*cis*-n-propyl, $R^{11}$=succinic acid mono ester) (1.16 mmol, 100%) as a white foam. The product was used without further purification.

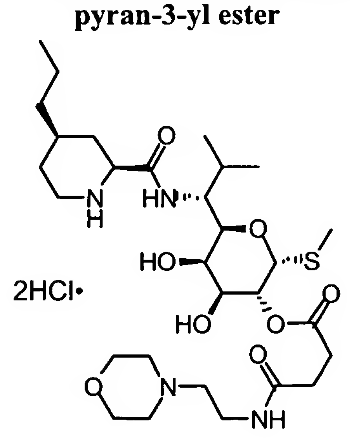
**[0637]** MS (ESPOS): 745.2 $[M + Na]^+$. MS (ESNEG): 721.2 $[M - H]^-$.

**[0638]** To a solution of protected succinate **18c** (wherein $R^1$=$R^2$ =Me, $R^3$=H, $R^9$=4-*cis*-n-propyl, $R^{11}$=succinic acid mono ester) (251 mg, 0.35 mmol, 1 equiv) in 1,2-dichloroethane (20 mL) at 23 °C was added $H_2O$ (1.0 mL) followed by TFA (8.0 mL). After stirring for 25 min at 23 °C, toluene (30 mL) was added and the resulting solution was concentrated to 20 mL volume. This solution was further diluted with toluene (30 mL) then concentrated to dryness. The product was purified by semi-preparative HPLC (Waters Nova-Pak® HR $C_{18}$, 6 µm particle size, 60 Å pore size, 20 mm ID × 100 mm, 5–60% acetonitrile in $H_2O$ w/ 0.1% AcOH over 30 min, 20 mL/min flow rate) to give 94 mg of the title compound as a white solid.

**[0639]** $^1$H NMR (300 MHz, $D_2O$) δ 5.55 (d, *J*=6.0, 1), 5.15 (dd, *J*=6.0, 10.5, 1), 4.26–4.16 (m, 2), 3.98–3.87 (m, 3), 3.51 (br d, *J*=13.5, 1), 3.07 (br t, *J*=9.9, 1), 2.69 (t, *J*=7.2, 2), 2.56 (t, *J*=7.2, 2), 2.28–2.21 (m, 1), 2.16–2.06 (m, 1), 2.13 (s, 3), 2.04–1.96 (m, 1), 1.84–1.70 (m, 1), 1.54–1.28 (m, 6), 0.94–0.84 (m, 9 H). MS (ESPOS): 505.1 $[M+H]^+$. MS (ESNEG): 503.2 $[M - H]^-$.

## Example 83

### Preparation of *N*-(2-Morpholin-4-yl-ethyl)-succinamic acid 4,5-dihydroxy-6-{2-methyl-1-[(4-propyl-piperidine-2-carbonyl)-amino]-propyl}-2-methylsulfanyl-tetrahydro-pyran-3-yl ester






pa-858557

[0640] To a solution of protected succinate **18c** (wherein $R^1$=$R^2$ =Me, $R^3$=H, $R^9$=4-*cis*-n-propyl, $R^{11}$=succinic acid mono ester) (222 mg, 0.31 mmol, 1 equiv) in DMF (3.0 mL) at 0 °C was added 4-(2-aminoethyl)morpholine (60 µL, 0.46 mmol, 1.5 equiv) followed by EDC•HCl (89 mg, 0.46 mmol, 1.5 equiv) followed by HOBt•$H_2O$ (56 mg, 0.37 mmol, 1.2 equiv). After stirring for 20 min at 0 °C the reaction was warmed to 23 °C. After stirring for a further 16 h, volatiles were removed in vacuo and the residue was partitioned between EtOAc (100 mL) and 1:1 brine/10% aqueous citric acid (100 mL). The organic layer was separated, washed with brine (80 mL), dried ($MgSO_4$) filtered and concentrated to furnish 242 mg (0.29 mmol, 94%) of **18c** (wherein $R^1$=$R^2$ =Me, $R^3$=H, $R^9$=4-*cis*-n-propyl, $R^{11}$=*N*-(2-Morpholin-4-yl-ethyl)-succinic acid mono ester) as a clear oil. The product was used without further purification.

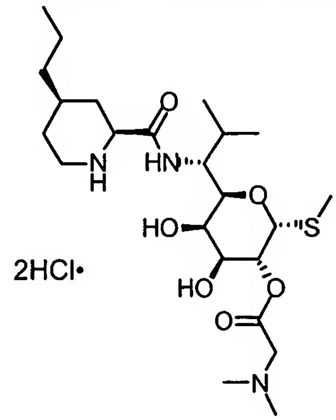
[0641] MS (ESPOS): 835.5 $[M+H]^+$.

[0642] To a solution of protected succinate **18c** (wherein $R^1$=$R^2$ =Me, $R^3$=H, $R^9$=4-*cis*-n-propyl, $R^{11}$=*N*-(2-Morpholin-4-yl-ethyl)-succinic acid mono ester) (242 mg, 0.29 mmol, 1 equiv) in 1,2-dichloroethane (20 mL) at 23 °C was added $H_2O$ (1.0 mL) followed by TFA (8.0 mL). After stirring for 25 min at 23 °C, toluene (70 mL) was added and the resulting solution was concentrated to dryness. The product was purified by semi-preparative HPLC (Waters Nova-Pak® HR $C_{18}$, 6 µm particle size, 60 Å pore size, 20 mm ID × 100 mm, 5–60% acetonitrile in $H_2O$ w/ 0.1% HCl over 30 min, 20 mL/min flow rate) to give 47 mg of the title compound as a white solid.

[0643] $^1$H NMR (300 MHz, $D_2O$) δ 5.52 (d, *J*=6.0, 1), 5.12 (dd, *J*=6.0, 10.5, 1), 4.24–4.16 (m, 2), 3.95–3.85 (m, 3), 3.63 (t, *J*=6.0, 2), 3.50 (br d, *J*=13.5, 1), 3.34 (t, *J*=6.0, 2), 3.05 (dt, *J*=3.0, 13.5, 1), 2.76 (t, *J*=6.0, 2), 2.61 (t, *J*=6.0, 2), 2.28–2.21 (m, 1), 2.16–2.06 (m, 1), 2.11 (s, 3), 2.04–1.96 (m, 1), 1.84–1.70 (m, 1), 1.54–1.28 (m, 6), 0.94–0.84 (m, 9 H); *morpholine protons are visible but very broad, causing baseline humps between δ 4.15–3.14 (8 H).* MS (ESPOS): 617.5 $[M+H]^+$. MS (ESNEG): 651.2 $[M + Cl]^-$.

### Example 84

**Preparation of Dimethylamino-acetic acid 4,5-dihydroxy-6-{2-methyl-1-[(4-propyl-piperidine-2-carbonyl)-amino]-propyl}-2-methylsulfanyl-tetrahydro-pyran-3-yl ester**



[0644] To a solution of alcohol **18b** (wherein $R^1=R^2$ =Me, $R^3$=H, $R^9$=4-*cis*-n-propyl, m=2) (393 mg, 0.63 mmol, 1 equiv) in $CH_2Cl_2$ (5.0 mL) at 23 ˚C was added *N,N*-dimethylglycine (72 mg, 0.70 mmol, 1.1 equiv) followed by DCC (390 mg, 1.90 mmol, 3 equiv) followed by DMAP (54 mg, 0.44 mmol, 0.7 equiv). After stirring for 12 h at 23 ˚C, the reaction mixture was filtered through a PTFE membrane (0.45 μm) with the aid of $CH_2Cl_2$ (20 mL). The filtrate was partitioned between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (80 mL). The organic layer was separated, washed with 1:1 brine:10% aqueous citric acid (60 mL), brine (50 mL), dried ($MgSO_4$) filtered and concentrated to furnish 600 mg of brown solid which was determined to contain the desired product. The crude product was used without further purification.

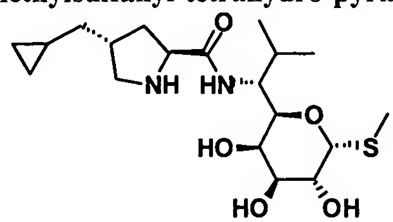
[0645] MS (ESPOS): 708.5 $[M+H]^+$.

[0646] To a solution of protected glycinate (600 mg, crude) in 1,2-dichloroethane (20 mL) at 23 ˚C was added $H_2O$ (1.0 mL) followed by TFA (8.0 mL). After stirring for 20 min at 23 ˚C, toluene (100 mL) was added and the resulting solution was concentrated to dryness. The residue was dissolved/suspended in $H_2O$ (10 mL) and filtered through a PTFE membrane (0.45 μm) with the aid of $H_2O$ (10 mL). The resulting solution was purified by semi-preparative HPLC (Waters Nova-Pak® HR $C_{18}$, 6 μm particle size, 60 Å pore size, 20 mm ID × 100 mm, 5–60% acetonitrile in $H_2O$ w/ 0.1% HCl over 30 min, 20 mL/min flow rate) to give 189 mg the title compound as a white solid.

[0647] $^1$H NMR (300 MHz, $D_2O$) δ 5.62 (d, *J*=6.3, 1), 5.30–5.23 (m, 1), 4.27–4.16 (m, 4), 3.95–3.89 (m, 3), 3.50 (br d, *J*=12.3, 1), 3.04 (br t, *J*=13.2, 1), 3.00 (s, 6), 2.28–2.19 (m, 1), 2.16–2.06 (m, 1), 2.13 (s, 3), 2.04–1.96 (m, 1), 1.84–1.70 (m, 1), 1.54–1.28 (m, 6), 0.93–0.83 (m, 9 H). MS (ESPOS): 490.4 $[M+H]^+$. MS (ESNEG): 524.2 $[M + Cl]^-$.

## Example 85

### Preparation of 4-Cyclopropylmethyl-pyrrolidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide



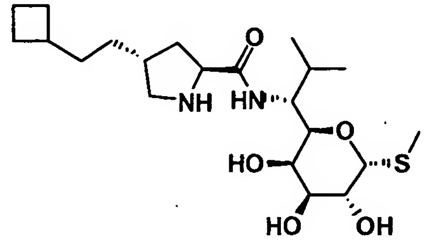
[0648] Amino acid intermediate (*2S, 4R*)-4-cyclopropylmethyl-pyrrolidine-1,2-dicarboxylic acid-1-*tert*-butyl ester was prepared by the synthetic sequence described by Goodman et al. *Journal of Organic Chemistry*, **2003**, *68*, 3923.

[0649] Lincosamine **2b** ($R^1$=Me, $R^2$=Me) was coupled to (*2S, 4R*)-4-cyclopropylmethyl-pyrrolidine-1,2-dicarboxylic acid-1-*tert*-butyl ester as depicted in general coupling scheme 11 to provide intermediate **11a** ($R^1$=$R^2$ =Me, $R^3$=H, $R^9$=cyclopropylmethyl, $P^1$=H, $P^2$=carboxylic acid-*t*-butyl ester, m=1) which was deprotected under acidic conditions to provide the title compound.

[0650] MS (ESPOS): 403.3 $[M+H]^+$.

## Example 86

### Preparation of 4-(2-Cyclobutyl-ethyl)-pyrrolidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide



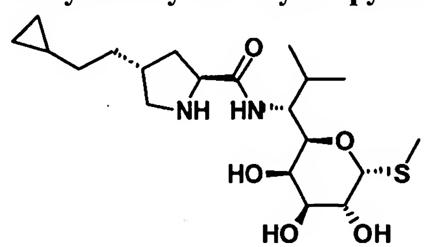
[0651] Amino acid intermediate (*2S, 4R*)-4-(2-cyclobutyl-ethyl)-pyrrolidine-1,2-dicarboxylic acid-1-*tert*-butyl ester was prepared by general method K by alkylation of pyroglutamic acid ester **7a** with (2-bromo-ethylidene)-cyclobutane. The allylic halide (2-bromo-ethylidene)-cyclobutane starting material was prepared from cyclobutanone in two steps as disclosed in U.S. patent 3,711,555.

[0652] Lincosamine **2b** ($R^1$=Me, $R^2$=Me) was coupled to protected amino acid **7d** ($R^9$=2-cyclobutyl-ethyl) to provide intermediate carbamate **11a** ($R^1$=$R^2$ =Me, $R^3$=H, $R^9$=2-cyclobutyl-ethyl, $P^1$=H, $P^2$=carboxylic acid-*t*-butyl ester, m=1) which was deprotected under acidic conditions to provide the title compound.

[0653] MS (ESPOS): 432.3 $[M+H]^+$.

## Example 87

### Preparation of 4-(2-Cyclopropyl-ethyl)-pyrrolidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide

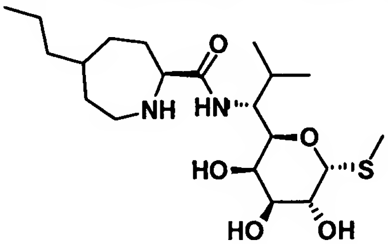



[0654] Lincosamine **2b** ($R^1$=Me, $R^2$=Me) was coupled to protected amino acid **8c** ($R^9$=2-cyclopropyl-ethyl) prepared by method M to provide intermediate carbamate **11a** ($R^1$=$R^2$ =Me, $R^3$=H, $R^9$= 2-cyclopropyl-ethyl, $P^1$=H, $P^2$=carboxylic acid-*t*-butyl ester, m=1) which was deprotected under acidic conditions to provide the title compound.

[0655] MS (ESPOS): 417.3 $[M+H]^+$.

## Example 88

### Preparation of 5-Propyl-azepane-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide



**[0656]** To a solution of protected cyclic amino acid **19f** ($R^{12}$=H, $R^{13}$=propyl), (81.4 mg, 0.29 mmol) prepared by general method W, DIEA (100 μL, 0.57 mmol) and **2b** ($R^1$=Me, $R^2$=Me) HCl salt (83 mg, 0.29 mmol) in anhydrous DMF (2 mL) and HBTU (120 mg, 0.32 mmol) were added. The resulting reaction mixture was stirred for 6 hours at room temperature under $N_2$ then concentrated to a residue. The residue was taken up in ethyl acetate and washed with 10% citric acid, saturated sodium bicarbonate, and brine. The organic layer was dried and evaporated to dryness to give the desired 1'-N protected lincosamide **11a** ($R^1$=Me, $R^2$=Me, $R^3$=H, $R^9$=propyl, $P^1$=H, $P^2$=carboxylic acid-*t*-butyl ester) (148 mg, 100 %).

**[0657]** To a solution of 1'-N protected lincosamide **11a** ($R^1$=Me, $R^2$=Me, $R^3$=H, $R^9$=propyl, $P^1$=H, $P^2$=carboxylic acid*t*-butyl ester) (147 mg, 0.285 mmol) in anhydrous DCE (2.0 mL) was added a solution of TES (10 μL, 0.13 mmol) in TFA (7.5% by weight water) 0.44 mL,). The resulting reaction mixture was stirred for one hour at room temperature under $N_2$. The reaction mixture was concentrated and co-evaporated with toluene to furnish the desired product 5-Propyl-2,3,6,7-tetrahydro-1*H*-azepine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide (151 mg, 100 %) as a white solid which was used in the subsequent reaction without further purification.

**[0658]** MS(ESPOS): 517 $[M+H]^+$.

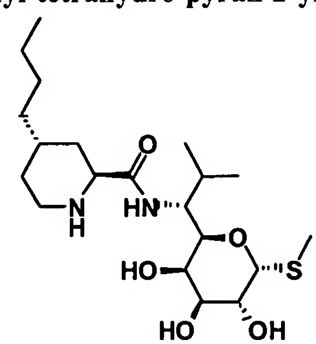
**[0659]** To a solution of 5-Propyl-2,3,6,7-tetrahydro-1*H*-azepine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide (112.4 mg, 0.212 mmol) in methanol (8.0 mL) was added 10% Pd/C degusa wet form (100 mg). The resulting suspension was hydrogenated at 50 psi for two days. The reaction mixture was filtered through celite, then a 0.45 μm PTFE membrane and evaporation to dryness to furnish the crude product (96 mg, 88 %). The crude product was purified by semi-preparative HPLC (Waters

Nova-Pak® HR $C_{18}$, 6 µm particle size, 60 Å pore size, 20 mm ID × 100 mm, 5–60% acetonitrile in $H_2O$ w/ 0.1% AcOH over 30 min, 20 mL/min flow rate) to provide the title compound (23.5 mg, 21.5 %) as a white solid.

**[0660]** $^1H$ NMR (300 MHz, $CD_3OD$) δ 5.24 (d, 1). 4.20-4.27 (m, 1), 4.04-4.15 (m, 2), 3.84 (d, 1), 3.41-3.55 (m, 2), 3.10-3.18 (t, 1), 1.88-2.20 (m, 6), 1.50-1.61 (m, 2), 1.25-1.39 (m, 3), 0.88-0.89 (m, 6); MS (ESPOS): 419.4 $[M+H]^+$.

## Example 89

### Preparation of 4-butyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide



**[0661]** Lincosamine **2b** ($R^1$=Me, $R^2$=Me) was coupled to amino acid intermediate **20o**, (wherein $R^{13}$=H, $R^{12}$=4-*trans*-n-butyl, n=1) as prepared by method X, as depicted in general coupling scheme 11 to provide intermediate carbamate **11a** ($R^1$=$R^2$ =Me, $R^3$=H, $R^9$=4-*trans*-n-butyl, $P^1$=H, $P^2$=carboxylic acid-*t*-butyl ester, m=2) which was deprotected under acidic conditions to provide the title compound.

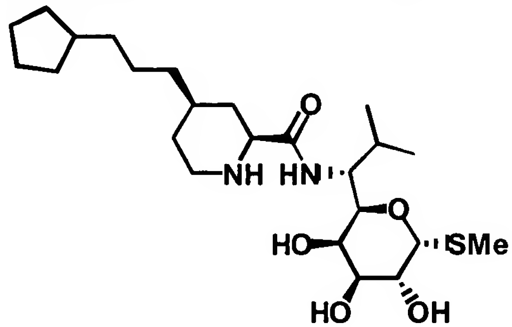
**[0662]** MS (ESPOS): 420 $[M+H]^+$.



pa-858557

## Example 90

**Preparation of 4-(3-Cyclopentyl-propyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**

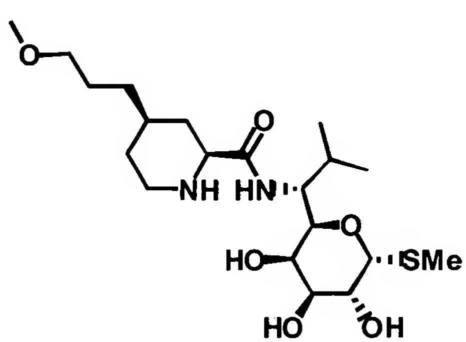


[0663] To a mixture of **13c** ($R^1$=$R^2$ =Me, $R^3$=H, $R^{9'}$=3-Cyclopentyl-prop-1-ynyl) prepared by method Q (100 mg, 0.22 mmol) in MeOH (6 mL) and water (4 mL) were added platinum oxide (200 mg) and conc. HCl (25 μL). The mixture was purged and charged with hydrogen (65 psi) and shaken overnight. The platinum oxide was removed by filtration and the filtrate was evaporated. The residue was purified by column chromatography to give the title compound (26.8 mg, 26%) as a white solid.

[0664] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, *J* = 5.4, 1), 4.17 (dd, *J* = 3.3, 10.2, 1), 4.10-4.03 (m, 2), 3.81 (d, *J* = 3.3, 1), 3.57-3.48 (m, 2), 3.27-3.20 (m, 1), 2.84-2.74 (m, 1), 2.19-2.13 (m, 1), 2.10 (s, 3), 2.07-2.00 (m, 1), 1.82-1.70 (m, 4), 1.64-1.50 (m, 5), 1.38-1.25 (m, 6), 1.23-1.04 (m, 4), 0.94-0.88 (m, 6). MS (ESPOS): 473.7 $[M+H]^+$.

## Example 91

**Preparation of 4-(3-Methoxy-propyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



[0665] To a dry flask was added **13b** ($R^1$=$R^2$ =Me, $R^3$=H) (130 mg, 0.27 mmol, 1 equiv), triphenylphosphine (45.3 mg, 0.17 mmol, 0.64 equiv), copper (I) iodide (32.9 mg, 0.17 mmol, 0.64 equiv), palladium acetate (19.4 mg, 0.086 mmol, 0.32 equiv) and triethylamine (1.5 mL). The mixture was deaerated with nitrogen, followed by addition of methyl propargyl ether (Aldrich) (114 μL, 1.35 mmol, 5 equiv). The mixture was stirred at 50 °C overnight. The solvent was removed under vacuum to give a dark residue. The residue was purified by column chromatography to give **13c** ($R^1$=$R^2$ =Me, $R^3$=H, $R^{9'}$=3-Methoxy-prop-1-ynyl) as a yellow syrup (105 mg, 92%).

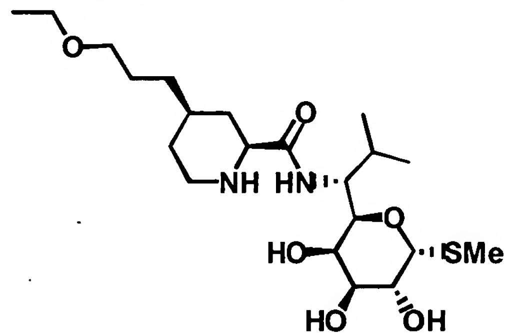
[0666] $^1$H NMR (300 MHz, $CDCl_3$) δ 8.52-8.49 (m, 1), 8.20 (bs, 1), 8.16 (s, 1), 7.46 (dd, $J$ = 1.7, 5.0, 1), 5.36 (d, $J$ = 5.4, 1), 5.03 (d, $J$ = 3, 1), 4.33 (s, 2), 4.27-4.10 (m, 2), 3.98 (d, $J$ = 10.2, 1), 3.75 (t, $J$ = 3.6, 1), 3.55-3.45 (m, 1), 3.44 (s, 3), 2.67 (d, $J$ = 9.9, 1), 2.47-2.40 (m, 1), 2.38 (d, $J$ = 5.1, 1), 2.17 (s, 3), 1.04 (d, $J$ = 7.2, 3), 0.96 (d, $J$ = 6.9, 3); MS (ESPOS): 425.6 $[M+H]^+$; MS (ESNEG): 423.5 $[M-H]^-$.

[0667] To a mixture of **13c** ($R^1$=Me, $R^{9'}$=3-Methoxy-prop-1-ynyl) (95 mg, 0.22 mmol) in MeOH (6 mL) and water (4 mL) were added platinum oxide (200 mg) and conc. HCl (26 μL). The mixture was purged and charged with hydrogen (65 psi) and shaken overnight. The platinum oxide was removed by filtration and the filtrate was evaporated. The residue was purified by chromatography to give the title compound (8 mg, 8 %) as a white solid.

[0668] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.23 (d, $J$ = 5.7, 1), 4.17 (dd, $J$ = 3.2, 10.1, 1), 4.10-4.02 (m, 2), 3.80 (d, $J$ = 3.3, 1), 3.53-3.43 (m, 2), 3.39 (t, $J$ = 6.5, 2), 3.31 (s, 3), 3.27-3.18 (m, 1), 2.80-2.70 (m, 1), 2.21-2.11 (m, 1), 2.10 (s, 3), 2.06-1.98 (m, 1), 1.82-1.74 (m, 1), 1.65-1.54 (m, 3), 1.38-1.28 (m, 2), 1.23-1.08 (m, 2), 0.93-0.88 (m, 6); MS (ESPOS): 435.7 $[M+H]^+$; MS (ESNEG): 433.6 $[M-H]^-$.

## Example 92

### Preparation of 4-(3-Ethoxy-propyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide



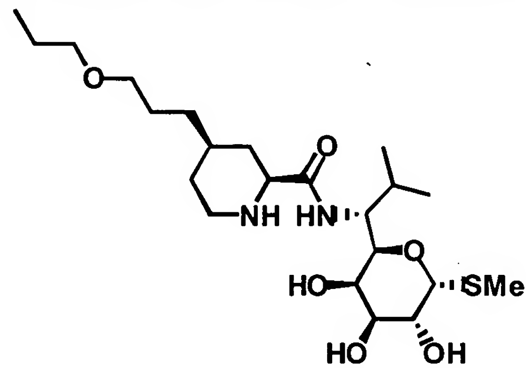
[0669] To a dry flask were added **13b** ($R^1$=$R^2$ =Me, $R^3$=H) made using method Q (130 mg, 0.27 mmol, 1 equiv), triphenylphosphine (45.3 mg, 0.17 mmol, 0.64 equiv), copper (I) iodide (32.9 mg, 0.17 mmol, 0.64 equiv), palladium acetate (19.4 mg, 0.086 mmol, 0.32 equiv) and triethylamine (1.5 mL). The mixture was deaerated with nitrogen, followed by addition of ethyl propargyl ether (113 mg, 1.35 mmol, 5 equiv). The mixture was stirred at 50 °C overnight. The solvent was removed under vacuum to give a dark residue. The residue was purified by chromatography to give **13c** ($R^1$=$R^2$ =Me, $R^3$=H, $R^{9'}$=3-Ethoxy-prop-1-ynyl) (78.1 mg, 66 %). MS (ESPOS): 439.6 $[M+H]^+$; MS (ESNEG): 437.5 $[M-H]^-$.

[0670] To a mixture of the above syrup in MeOH (6 mL) and water (4 mL) were added platinum oxide (150 mg) and conc. HCl (14 µL). The mixture was purged and charged with hydrogen (65 psi) and shaken overnight. The platinum oxide was removed by filtration and the filtrate was evaporated. The residue was purified by chromatography to give the title compound (20 mg, 25 %) as a white solid.

[0671] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.25 (d, $J$ = 5.7, 1), 4.21 (dd, $J$ = 3, 9.9, 1), 4.11-4.04 (m, 2), 3.89-3.80 (m, 2), 3.54-3.38 (m, 6), 3.10-2.98 (m, 1), 2.25-2.12 (m, 2), 2.11 (s, 3), 2.00-1.90 (m, 1), 1.78-1.56 (m, 2), 1.44-1.27 (m, 5), 1.17 (t, $J$ = 6.9, 3), 0.94-0.88 (m, 6). MS (ESPOS): 449.6 $[M+H]^+$; MS (ESNEG): 447.7 $[M-H]^-$.

## Example 93

**Preparation of 4-(3-Propoxy-propyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



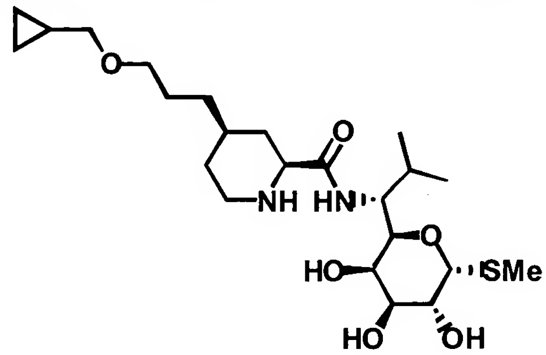
[0672] To a dry flask were added **13b** ($R^1$=$R^2$ =Me, $R^3$=H) made using method Q (150 mg, 0.31 mmol, 1 equiv), triphenylphosphine (52.4 mg, 0.2 mmol, 0.64 equiv), copper (I) iodide (38.1 mg, 0.2 mmol, 0.64 equiv), palladium acetate (22.4 mg, 0.1 mmol, 0.32 equiv) and triethylamine (1.7 mL). The mixture was deaerated with nitrogen, followed by addition of propargyl ether (117 mg, 1.24 mmol, 4 equiv). The mixture was stirred at 50 °C overnight. The solvent was removed under vacuum to give a dark residue. The residue was purified by chromatography to give **13c** ($R^1$=$R^2$ =Me, $R^3$=H, $R^{9'}$=3-prop-1-ynyl-oxy-prop-1-ynyl) (40.9 mg, 29 %). MS (ESPOS): 449.2 $[M+H]^+$.

[0673] To a mixture of the above syrup in MeOH (6 mL) and water (4 mL) were added platinum oxide (100 mg) and 0.1037 N HCl (0.86 mL, 0.089 mmol, 0.98 equiv). The mixture was purged and charged with hydrogen (65 psi) and shaken overnight. The platinum oxide was removed by filtration and the filtrate was evaporated. The residue was purified by chromatography to give a white solid, the title compound (11 mg, 26 %).

[0674] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, $J$ = 5.7, 1), 4.17 (dd, $J$ = 3.2, 10.1, 1), 4.10-4.02 (m, 2), 3.79 (d, $J$ = 3, 1), 3.53-3.32 (m, 6), 3.25-3.18 (m, 1), 2.80-2.68 (m, 1), 2.22-2.12 (m, 1), 2.10 (s, 3), 2.06-1.98 (m, 1), 1.83-1.74 (m, 1), 1.66-1.08 (m, 9), 0.97-0.86 (m, 9); MS (ESPOS): 463.4 $[M+H]^+$.

## Example 94

**Preparation of 4-(3-Cyclopropylmethoxy-propyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



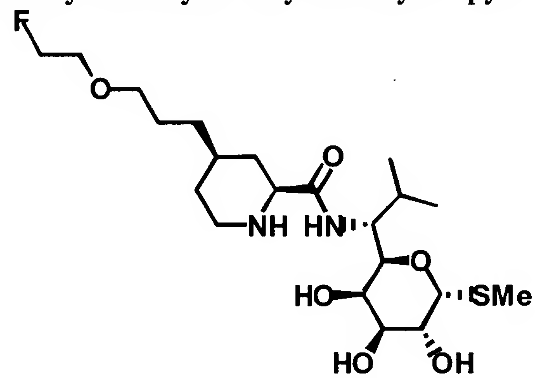
[0675] To a dry flask were added **13b** ($R^1$=$R^2$ =Me, $R^3$=H) made using method Q (200 mg, 0.42 mmol, 1 equiv), triphenylphosphine (69.7 mg, 0.27 mmol, 0.64 equiv), copper (I) iodide (50.6 mg, 0.27 mmol, 0.64 equiv), palladium acetate (29.8 mg, 0.13 mmol, 0.32 equiv) and triethylamine (2.4 mL). The mixture was deaerated with nitrogen, followed by addition of prop-2-ynyloxymethyl-cyclopropane (229 mg, 2.08 mmol, 5 equiv). The mixture was stirred at 50 °C overnight. The solvent was removed under vacuum to give a dark residue. The residue was purified by chromatography to give a **13c** ($R^1$=$R^2$ =Me, $R^3$=H, $R^{9'}$=3-Prop-2-ynyloxymethyl-cyclopropane) (113 mg, 59 %). MS (ESPOS): 465.1 $[M+H]^+$.

[0676] To a mixture of **13c** ($R^1$=$R^2$ =Me, $R^3$=H, $R^{9'}$=3-Prop-2-ynyloxymethyl-cyclopropane) in MeOH (6 mL) and water (4 mL) were added platinum oxide (230 mg) and conc. HCl (19.3 µL, 0.232 mmol, 0.95 equiv). The mixture was purged and charged with hydrogen (65 psi) and shaken overnight. The platinum oxide was removed by filtration and the filtrate was evaporated. The residue was purified by chromatography to give a white solid, the title compound (20 mg, 17 %).

[0677] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.25 (d, $J$ = 5.7, 1), 4.21 (dd, $J$ = 3.6, 9.9, 1), 4.11-4.04 (m, 2), 3.87-3.78 (m, 2), 3.54-3.38 (m, 4), 3.08-2.98 (m, 1), 2.27-2.07 (m, 2), 2.11 (s, 3), 2.01-1.91 (m, 1), 1.80-1.25 (m, 9), 1.01-0.85 (m, 7), 0.56-0.47 (m, 2), 0.22-0.15 (m, 2); MS (ESPOS): 475.2 $[M+H]^+$.

## Example 95

**Preparation of 4-[3-(2-Fluoro-ethoxy)-propyl]-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



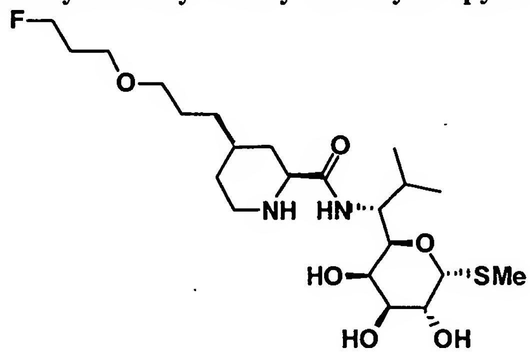
[0678] To a dry flask were added **13b** ($R^1$=$R^2$ =Me, $R^3$=H) made using method Q (230 mg, 0.48 mmol, 1 equiv), triphenylphosphine (80.1 mg, 0.31 mmol, 0.64 equiv), copper (I) iodide (58.2 mg, 0.31 mmol, 0.64 equiv), palladium acetate (34.2 mg, 0.15 mmol, 0.32 equiv) and triethylamine (2.7 mL). The mixture was deaerated with nitrogen, followed by addition of 3-(2-Fluoro-ethoxy)-propyne (244 mg, 2.39 mmol, 5 equiv). The mixture was stirred at 50 °C overnight. The solvent was removed under vacuum to give a dark residue. The residue was purified by chromatography to give **13c** ($R^1$=$R^2$ =Me, $R^3$=H, $R^{9'}$=3-(2-Fluoro-ethoxy)-propyne) (159 mg, 73%).

[0679] To a mixture of **13c** ($R^1$=$R^2$ =Me, $R^3$=H, $R^{9'}$=3-(2-Fluoro-ethoxy)-propyne) (159 mg, 73 %). in MeOH (6 mL) and water (4 mL) were added platinum oxide (320 mg) and conc. HCl (27.7 μL, 0.33 mmol, 0.95 equiv). The mixture was purged and charged with hydrogen (65 psi) and shaken overnight. The platinum oxide was removed by filtration and the filtrate was evaporated. The residue was purified by chromatography to give a white solid, the title compound (25 mg, 15%).

[0680] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, $J$ = 5.7, 1), 4.60-4.56 (m, 1), 4.44-4.39 (m, 1), 4.20 (dd, $J$ = 3.3, 9.9, 1), 4.10-4.04 (m, 2), 3.81-3.75 (m, 2), 3.73-3.68 (m, 1), 3.63-3.58 (m, 1), 3.54-3.48 (m, 3), 3.43-3.34 (m, 1), 3.04-2.93 (m, 1), 2.23-2.12 (m, 2), 2.11 (s, 3), 1.98-1.88 (m, 1), 1.78-1.25 (m, 7), 0.95-0.87 (m, 6). MS (ESPOS): 467.2 $[M+H]^+$.

## Example 96

**Preparation of 4-[3-(3-Fluoro-propoxy)-propyl]-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



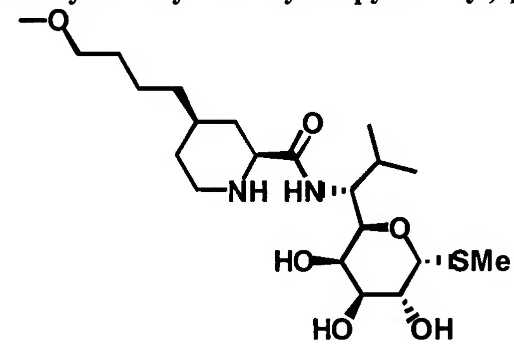
[0681] To a dry flask were added **13b** ($R^1$=$R^2$ =Me, $R^3$=H) made using method Q (230 mg, 0.48 mmol, 1 equiv), triphenylphosphine (80.1 mg, 0.31 mmol, 0.64 equiv), copper (I) iodide (58.2 mg, 0.31 mmol, 0.64 equiv), palladium acetate (34.2 mg, 0.15 mmol, 0.32 equiv) and triethylamine (2.7 mL). The mixture was deaerated with nitrogen, followed by addition of 3-(3-Fluoro-propoxy)-propyne (277 mg, 2.39 mmol, 5 equiv). The mixture was stirred at 50 °C overnight. The solvent was removed under vacuum to give a dark residue. The residue was purified by chromatography to give **13c** ($R^1$=$R^2$ =Me, $R^3$=H, $R^{9'}$=3-(3-Fluoro-propoxy)-propyne) (137 mg, 61 %).

[0682] To a mixture of the **13c** ($R^1$=$R^2$ =Me, $R^3$=H, $R^{9'}$=3-(3-Fluoro-propoxy)-propyne) in MeOH (6 mL) and water (4 mL) were added platinum oxide (280 mg) and conc. HCl (23.1 μL, 0.28 mmol, 0.95 equiv). The mixture was purged and charged with hydrogen (65 psi) and shaken overnight. The platinum oxide was removed by filtration and the filtrate was evaporated. The residue was purified by chromatography to give a white solid, the title compound (23 mg, 16 %).

[0683] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, $J$ = 5.7, 1), 4.57 (t, $J$ = 5.9, 1), 4.41 (t, $J$ = 6, 1), 4.20 (dd, $J$ = 3.2, 10.1, 1), 4.10-4.04 (m, 2), 3.81 (d, $J$ = 3, 1), 3.74-3.67 (m, 1), 3.55-3.42 (m, 5), 3.38-3.32 (m, 1), 2.98-2.87 (m, 1), 2.23-2.08 (m, 2), 2.11 (s, 3), 2.00-1.83 (m, 3), 1.72-1.57 (m, 2), 1.42-1.20 (m, 5), 0.97-0.87 (m, 6). MS (ESPOS): 481.2 $[M+H]^+$.

## Example 97

### Preparation of 4-(4-Methoxy-butyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide



[0684] To a mixture of NaH (60 %, 37.6 mg, 0.94 mmol, 1 equiv) in dry DMF (2 mL) at 0 °C was added a solution of **14c** ($R^9$=4-methoxybutyl) prepared by method R (197 mg, 0.94 mmol, 1 equiv) in DMF (0.5 mL) dropwise. The mixture was stirred at 0 °C for 20 min, then was cooled to -78° C. To the mixture was added iodomethane (134 mg, 0.94 mmol, 1 equiv). The mixture was stirred at 0°C for 2 hr, then at rt overnight. The reaction mixture was diluted with DCM, washed with brine, dried and concentrated. The residue was purified by preparative TLC to give 4-(4-Methoxy-butyl)-pyridine-2-carboxylic acid methyl ester (43 mg, 21%).

[0685] $^1$H NMR (300 MHz, $CDCl_3$) δ 8.61-8.58 (m, 1), 7.97-7.95 (m, 1), 7.29-7.26 (m, 1), 3.98 (s, 3), 3.37 (t, $J$ = 6, 2), 3.30 (s, 3), 2.70 (t, $J$ = 7.7, 2), 1.78-1.54 (m, 4).

[0686] To a mixture of 4-(4-Methoxy-butyl)-pyridine-2-carboxylic acid methyl ester ( (107 mg, 0.48 mmol, 1 equiv) in THF (1.5 mL) and water (0.5 mL) was added lithium hydroxide monohydrate (30.2 mg, 0.72 mmol, 1.5 equiv). The mixture was stirred at rt for 4 h and diluted with methanol (20 mL). Then $H^+$ resin (0.4 g) was added and the mixture was shaken for 10 minutes. The resin was washed with methanol (1x), 1:1 acetonitrile/water (1x), and acetonitrile (1x). The product was eluted with 5% TEA in methanol (4x) and acetonitrile (1x). The combined organic solvents were evaporated and co-evaporated with toluene to give 4-(4-Methoxy-butyl)-pyridine-2-carboxylic acid (63.4 mg, 63 %): $^1$H NMR (300 MHz, $CD_3OD$) δ 8.47-8.43 (m, 1), 7.98-7.94 (m, 1), 7.43-7.37 (m, 1), 3.41 (t, $J$ = 6.3, 2), 3.30 (s, 3), 2.75 (t, $J$ = 7.5, 2), 1.80-1.55 (m, 4).

[0687] To a solution of 4-(4-Methoxy-butyl)-pyridine-2-carboxylic acid (63.4 mg) in dry DMF (0.75 mL) at 0 °C were added a mixture of 7-Me MTL HCl salt **2b** ($R^1$=Me, $R^2$=Me) (87.3 mg, 0.30 mmol, 1 equiv) and DIEA (78 mg, 0.61 mmol, 2 equiv) in DMF (0.75 mL), followed by the addition of HBTU (100 mg, 0.73 mmol, 1 equiv). The reaction mixture was stirred at rt

for 3 h. The reaction mixture was evaporated under high vacuum to dryness. The residue was purified by chromatography to give a syrup (88 mg, 65 %).

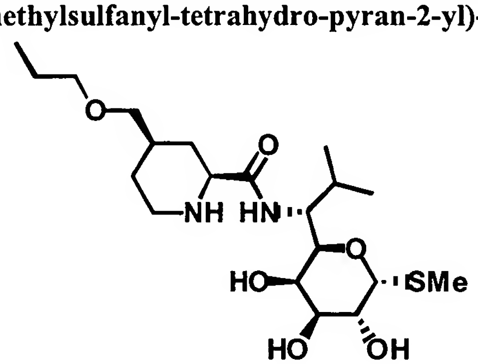
[0688] MS (ESPOS): 443.0 $[M+H]^+$; MS (ESNEG): 441.2 $[M-H]^-$.

[0689] To a mixture of the above syrup (88 mg, 0.20 mmol, 1 equiv) in MeOH (6 mL) and water (4 mL) were added conc. HCl (15.7 µL, 0.19 mmol, 0.95 equiv) and platinum oxide (180 mg). The mixture was purged and charged with hydrogen (65 psi) and shaken overnight. The platinum oxide was removed by filtration and the filtrate was evaporated to give a residue, which was purified by chromatography to provide the title compound (lower isomer, 20 mg, 22%) as a white solid.

[0690] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.22 (d, $J$ = 5.7, 1), 4.15 (dd, $J$ = 3.2, 10.1, 1), 4.09-4.00 (m, 2), 3.78 (d, $J$ = 2.7, 1), 3.49 (dd, $J$ = 3.3, 10.5, 1), 3.38 (t, $J$ = 6.3, 2), 3.30 (s, 3), 3.26-3.22 (m, 1), 3.16-3.08 (m, 1), 2.66-2.55 (m, 1), 2.20-2.11 (m, 1), 2.09 (s, 3), 1.96-1.87 (m, 1), 1.73-1.64 (m, 1), 1.58-1.22 (m, 7), 1.11-0.97 (m, 2), 0.93-0.86 (m, 6); MS (ESPOS): 449.4 $[M+H]^+$; MS (ESNEG): 447.2 $[M-H]^-$.

## Example 98

### Preparation of 4-Propoxymethyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide




[0691] To (1-Oxy-pyridin-4-yl)-methanol (5g, 0.04 mol) in a solution of dichloromethane (10 mL) and pyridine (10 mL) was added acetic anhydride (12.2 mL, 0.12 mol) and the reaction mixture was stirred for 16 h at room temperature. The reaction mixture was then poured into water and extracted with dichloromethane (200 mL) and then washed with brine (100 mL). The crude product obtained (4.27 g, 64%) was taken without purification for the next reaction. To the crude product (4.27 g, 25.6 mmol) in DCM (25 mL) and trimethylsilyl cyanide (3.40 mL, 25.6 mmol), dimethylcarbamyl chloride (2.35 mL, 25.6 mmol) was added slowly and then the reaction mixture was stirred at room temperature over night. Aqueous potassium carbonate (100

mL, 10%) was added and stirred for 10 minutes. Extraction with ethyl acetate followed by removal of solvent resulted in crude product which was purified on silica gel column chromatography using 50% ethyl acetate in hexanes to obtain cyanopyridine **10a** ($R^9$ = acetoxymethylene) (2.37 g, 48%).

**[0692]** $^1$H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, $J$ = 5.7 Hz, 1), 7.65 (s, 1), 7.45 (d, $J$ = 5.7 Hz, 1), 5.13 (s, 2), 2.16 (s, 3). MS (ESPOS): 199 $[M+Na]^+$.

**[0693]** To acetic acid 2-cyano-pyridin-4-ylmethyl ester **10a** ($R^9$ = acetoxymethylene) (2.37 g, 0.012 mol), aqueous hydrochloric acid (50 mL, 6N) was added and refluxed for 16 hr. Stripping off hydrochloric acid and water resulted in acid **10b** ($R^9$ = acetoxymethylene) (2.47 g, 100%).

**[0694]** $^1$H NMR (300 MHz, $CD_3OD$) δ 8.83 (d, $J$ = 5.7 Hz, 1), 8:56 (s, 1), 8.24 (d, $J$ = 5.7 Hz, 1), 4.92 (s, 2 MS (ESNEG): 152 $[M-H]^-$.

**[0695]** To the **10b** ($R^9$ = acetoxymethylene) (2.40 g, 0.012 mol) in methanol (25 mL), water (15 mL) and acetic acid (15 mL), platinum dioxide (1 g) was added and hydrogenated at 50 *psi* for 16 h. The catalyst was filtered and the solvent was removed to obtain the hydrogenated product (2.50 g, 100%) which was taken as such for the next reaction. To the crude product from previous reaction in dioxane (30 mL) and water (30 mL), sodium hydroxide (2.2 g, 0.05 mol) and di *t*-butyldicarbonate (12 g, 0.05 mol) was added and stirred at room temperature for 16 h. The reaction mixture was then extracted with ethyl acetate (100 mL) to remove any excess Boc-anhydride. The aqueous phase was then carefully acidified with dil. HCl (1N) and extracted with ethyl acetate. The crude product obtained on removal of solvent was purified on silica gel column chromatography using ethyl acetate to obtain the 4-hydroxymethyl-piperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (0.62 g, 20%).

**[0696]** $^1$H NMR (300 MHz, $CD_3OD$) δ 4.27 (d, $J$ = 6.3 Hz, 1), 3.37-3.65 (m, 4), 2.05 (m, 1), 1.70-1.84 (m, 4), 1.52 (s, 9). MS (ESNEG): 258 $[M-H]^-$.

**[0697]** To the 4-hydroxymethyl-piperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (100 mg, 0.39 mmol) in DMF (5 mL), sodium hydride (30 mg, 0.67 mmol) was added and stirred at 0 °C for 10 minutes. Propyl bromide (0.5 mL, 4.0 mmol) (0.5 mL, 0.35 mmol) was added and stirred at room temperature for 30 minutes and then at 50-60 °C for 2 h. DMF was removed, water (50 mL) was added and extracted with ethyl acetate (50 mL). The product obtained on removal of solvent was purified on column chromatography using 50% ethyl acetate in hexanes to provide 4-Butoxymethyl-piperidine-1,2-dicarboxylic acid 2-butyl ester 1-*tert*-butyl ester (100 mg, 75%).

[0698] $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.10 (q, $J$ = 6.6, 7.2 Hz, 4), 3.46-3.53 (m, 2), 3.25-3.36 (m, 2), 2.05 (m, 2), 1.44-1.75 (m, 6), 1.45 (s, 9), 0.88-0.98 (m, 6). MS (ESPOS): 366 $[M+Na]^+$.

[0699] To the 4-Butoxymethyl-piperidine-1,2-dicarboxylic acid 2-butyl ester 1-*tert*-butyl ester (100 mg, 0.29 mmol) in THF (5 mL), lithium hydroxide (122 mg, 2.90 mmol) in water (1 mL) was added and stirred at room temperature for 16 h. It was then poured into water and extracted with ethyl acetate and discarded. The water layer was acidified and then extracted with ethyl acetate (50 mL). Removal of solvent gave the acid which was taken as such for the next coupling reaction. To 4-Butoxymethyl-piperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (88 mg, 0.29 mmol) in DMF (3 mL), the amine **2b** ($R^1$=Me, $R^2$=Me) (100 mg, 0.34 mmol), HBTU (132 mg, 0.34 mmol) and DIEA (0.1 mL, 0.58 mmol) was added and stirred at room temperature for 3 h. DMF was removed and product was purified on silica gel column chromatography using 50% ethyl acetate in hexanes provided the Boc protected lincosamide ($R^9$ = 4-Butoxymethyl) (77 mg, 49%).

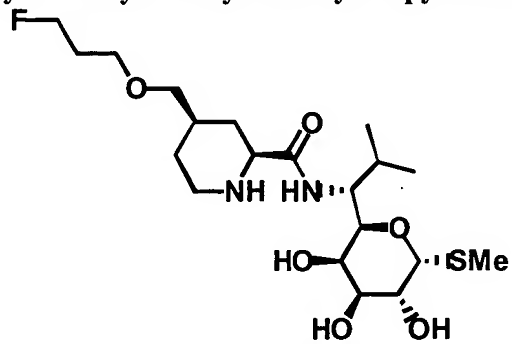
[0700] $^1H$ NMR (300 MHz, $CD_3OD$) δ 5.25 (m, 1), 4.47-4.64 (m, 2), 4.41 (t, $J$ = 6.0 Hz, 1), 4.26 (s, 1), 3.99-4.12 (m, 4), 3.85 (d, $J$ = 3.3 Hz, 1), 3.50-3.54 (m, 2), 3.31-3.36 (m, 2), 2.14-2.2.19 (m, 2), 1.81 (m, 3), 1.53 (m, 2), 1.45 (bs, 12), 0.88-0.98 (m, 9). MS (ESPOS): 535 $[M+H]^+$.

[0701] To the above Boc protected lincosamide ($R^9$ = 4-Butoxymethyl) (77 mg, 0.14 mmol), 30% TFA in DCE (30 mL), triethylsilane (1 mL) and water (1 mL) was added and stirred at room temperature for 1 hr. The residue obtained on removing the solvent was chromatographed using 20% methanol in DCM to obtain the title compound (10 mg, 16%) as a white solid.

[0702] $^1H$ NMR (300 MHz, $CD_3OD$) δ 5.25 (d, $J$ = 5.7 Hz, 1), 4.05-4.19 (m, 3), 3.74-3.86 (m, 2), 3.50-3.54 (m, 2), 3.40-3.54 (m, 4), 2.14 (m, 2), 2.10 (s, 3), 2.00 (m, 1), 1.71-1.75 (m, 2), 1.54-1.61 (m, 2), 1.31 (m, 1), 0.89-0.94 (m, 9). MS (ESPOS): 435 $[M+H]^+$.

## Example 99

**Preparation of 4-(3-Fluoro-propoxymethyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**

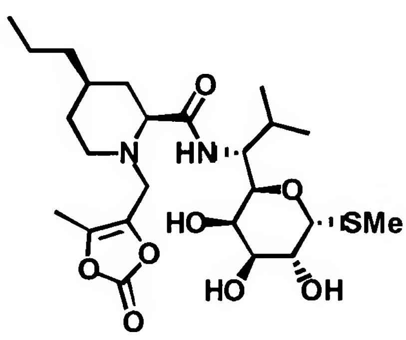


[0703] The title compound was prepared by the same reaction sequence described in example **98** starting from Boc protected 4-hydroxymethyl-piperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester substituting the reagent 3-fluoropropyl bromide in the alkylation.

[0704] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.22 (d, $J$ = 5.4 Hz, 1), 4.58 (q, $J$ = 3.9, 6.9 Hz, 1), 4.22 (q, $J$ = 5.1, 5.7 Hz, 1), 3.90-4.16 (m, 3), 3.82-3.86 (m, 1), 3.74 (d, $J$ = 2.1 Hz, 1), 3.47-3.59 (m, 3), 3.35-3.39 (m, 1), 3.04 (m, 2), 2.07 (s, 3), 1.85-1.98 (m, 4), 1.47-1.56 (m, 2), 1.02-1.12 (m, 2), 0.90-0.96 (m, 6). MS (ESPOS): 453 $[M+H]^+$.

## Example 100

**Preparation of 1-(5-Methyl-2-oxo-[1,3]dioxol-4-ylmethyl)-4-propyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



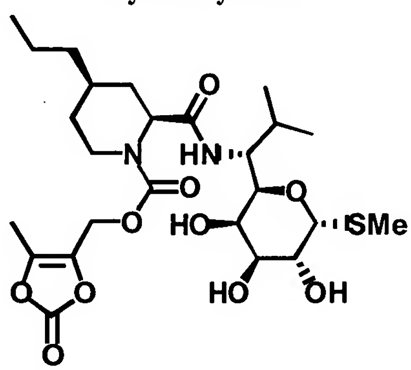
[0705] To the title compound from example **17** (50 mg, 0.123 mmol) in DMF (5 mL) at room temperature, sodium carbonate (25 mg, 0.246 mmol) and bromomethyl dioxalenone, prepared as described in J. Alexander, *et.al. J. Med. Chem*, **1996**, *39*, 480-486. (47 mg, 0.246 mmol) were added and stirred over night at room temperature. DMF was removed and the crude

material was loaded into a silica gel column and eluted with a mixture of methanol (5%) and dichloromethane to obtain the title compound as a white solid (30 mg, 48%).

**[0706]** TLC: $R_f$ = 0.5 (EtOAc). MS (ESPOS):517 $[M+H]^+$; $^1H$ NMR ($CD_3OD$, 200 MHz): δ 5.22 (d, *J* = 3.8 Hz, 1), 4.05-4.20 (m, 3), 3.86 (d, *J* = 2 Hz, 1), 3.51-3.60 (m, 2), 2.88-3.01 (m, 2), 2.17 (m, 2), 2.13 (s, 3), 2.10 (s, 3), 1.88 (d, *J* = 6.2 Hz, 1), 1.70 (d, *J* = 8.2 Hz, 1), 1.21-1.35 (m, 6), 0.90-0.96 (m, 9).

## Example 101

**Preparation of 2-[2-Methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propylcarbamoyl]-4-propyl-piperidine-1-carboxylic acid 5-methyl-2-oxo-[1,3]dioxol-4-ylmethyl ester**

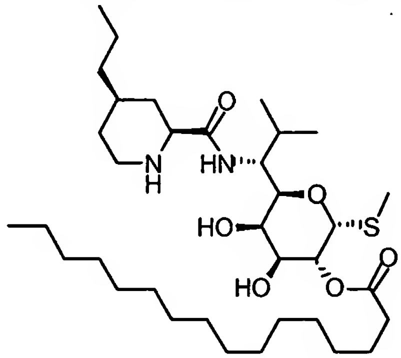



**[0707]** To the title compound from example **17** (50 mg, 0.123 mmol) in DMF (5 mL) at room temperature, potassium bicarbonate (20 mg, 0.30 mmol) and *p*-nitrophenyl dioxalenone, prepared as described in F. Sakamoto, *et.al*, *Chem. Pharm. Bull.* **1984**, *32* (6), 2241-2348. (36 mg, 0.123 mmol) were added and stirred over night at room temperature. DMF was removed and the crude material was loaded into a silica gel column and eluted with a mixture of methanol (5%) and dichloromethane to obtain the title compound (30 mg, 44%) as a white solid.

**[0708]** TLC: Rf = 0.5 (EtOAc). MS (ESPOS):561 $[M+H]^+$; $^1H$ NMR ($CD_3OD$, 200 MHz): δ 5.23 (d, *J* = 3.8 Hz, 1), 4.92 (m, 2), 4.21-4.24 (m, 1), 4.07-4.13 (m, 3), 3.98 (m, 1), 3.57 (d, *J* = 2.2 Hz, 1), 3.54 (d, *J* = 2.2 Hz, 1), 2.16 (s, 3), 2.08 (s, 3), 1.95-1.97 (m, 2), 1.76-1.85 (m, 2), 1.60 (m, 1), 1.32 (m, 4), 0.88-0.98 (m, 9).

## Example 102

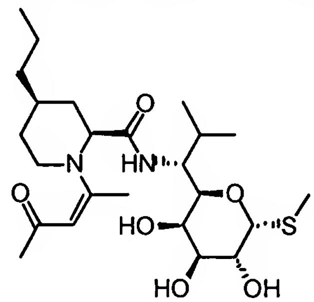
**Preparation of Hexadecanoic acid 4,5-dihydroxy-6-{2-methyl-1-[(4-propyl-piperidine-2-carbonyl)-amino]-propyl}-2-methylsulfanyl-tetrahydro-pyran-3-yl ester**



[0709] The title compound, **5** (wherein $R^1$=$R^2$ =Me, $R^3$=H, $R^6$=H, $R^9$=4-*cis*-n-propyl, $R^{11}$=$CO(CH_2)_{14}CH_3$, m=2) may be prepared employing method V by treatment of alcohol **18b** (wherein $R^1$=$R^2$=Me, $R^3$=H, $R^6$=Boc, $R^9$=4-cis-n-Pr, and m=2) with the acylating reagent palmitoyl chloride.

## Example 103

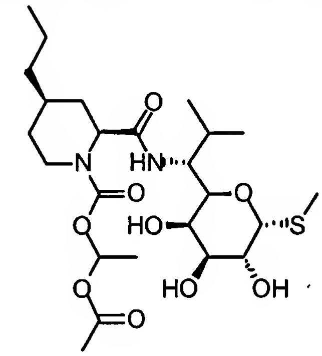
**Preparation of 1-(1-Methyl-3-oxo-but-1-enyl)-4-propyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



[0710] The title compound may be prepared employing the method described by Jensen et al, Journal of Medicinal Chemistry **1980**, 23, by treatment of **1** (wherein $R^1$=$R^2$=Me, $R^3$=H, $R^6$=H, $R^9$=4-cis-n-propyl, and m=2) with acetylacetone.

## Example 104

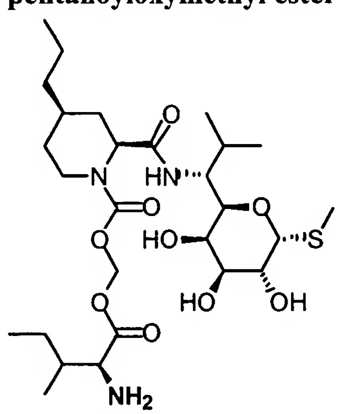
**Preparation of 2-[2-Methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propylcarbamoyl]-4-propyl-piperidine-1-carboxylic acid 1-acetoxy-ethyl ester**



[0711] The title compound may be prepared employing the method described by Alexander et al, Journal of Medicinal Chemistry **1988**, 31, 318–322, by treatment of **1** (wherein $R^1$=$R^2$=Me, $R^3$=H, $R^6$=H, $R^9$=4-cis-n-propyl, and m=2) with the acylating reagent Acetic acid 1-(4-nitro-phenoxycarbonyloxy)-ethyl ester.

## Example 105

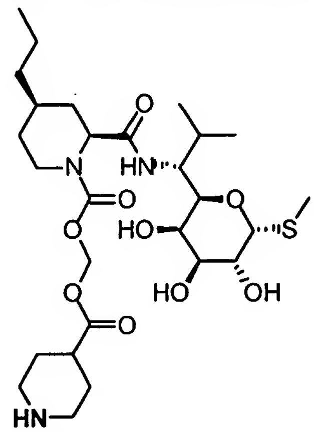
**Preparation of 2-[2-Methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propylcarbamoyl]-4-propyl-piperidine-1-carboxylic acid 2-amino-3-methyl-pentanoyloxymethyl ester**



[0712] The title compound may be prepared employing the method described by Alexander et al, Journal of Medicinal Chemistry **1988**, 31, 318–322, by treatment of **1** (wherein $R^1$=$R^2$=Me, $R^3$=H, $R^6$=H, $R^9$=4-cis-n-propyl, and m=2) with the appropriate acylating reagent (2-tert-butoxycarbonylamino-3-methyl-pentanoic acid 4-nitro-phenoxycarbonyloxymethyl ester), followed by TFA deprotection.

## Example 106

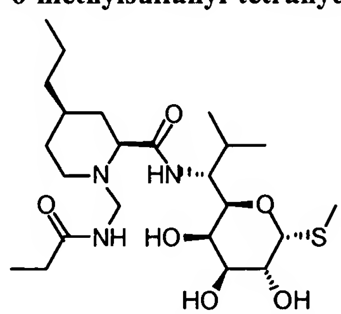
### Preparation of 2-[2-Methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propylcarbamoyl]-4-propyl-piperidine-1-carboxylic acid piperidine-4-carbonyloxymethyl ester



[0713] The title compound may be prepared employing the method described by Alexander et al, Journal of Medicinal Chemistry **1988**, 31, 318–322, by treatment of **1** (wherein $R^1$=$R^2$=Me, $R^3$=H, $R^6$=H, $R^9$=4-cis-n-propyl, and m=2) with the appropriate acylating reagent (piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-(4-nitro-phenoxycarbonyloxymethyl) ester), followed by TFA deprotection.

## Example 107

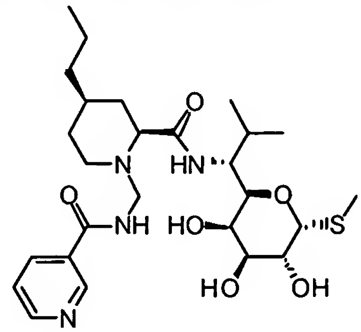
### Preparation of 1-(Propionylamino-methyl)-4-propyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide



[0714] The title compound may be prepared from **1** (wherein $R^1$=$R^2$=Me, $R^3$=H, $R^6$=H, $R^9$=4-cis-n-propyl, and m=2) employing the method described by Bundgaard et al, Journal of Pharmaceutical Sciences, **1980**, 69 (1), 44–46.

## Example 108

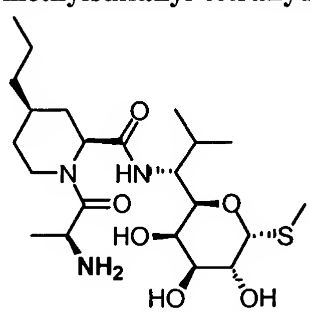
**Preparation of N-{2-[2-Methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propylcarbamoyl]-4-propyl-piperidin-1-ylmethyl}-nicotinamide**



[0715] The title compound may be prepared from **1** (wherein $R^1$=$R^2$=Me, $R^3$=H, $R^6$=H, $R^9$=4-cis-n-propyl, and m=2) employing the method described by Bundgaard et al, Journal of Pharmaceutical Sciences, **1980**, 69 (1), 44–46.

## Example 109

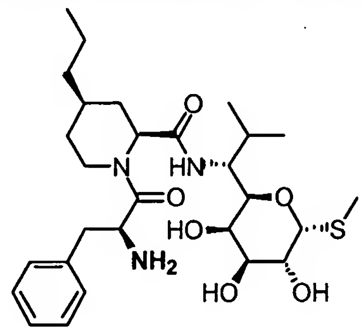
**Preparation of 1-(2-Amino-propionyl)-4-propyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



[0716] The title compound may be prepared employing the method described by Weiss et al, Antimicrobial Agents and Chemotherapy, **1999**, 43 (3), 460–464, by treatment of **1** (wherein $R^1$=$R^2$=Me, $R^3$=H, $R^6$=H, $R^9$=4-cis-n-propyl, and m=2) with Boc-alanine and HATU in the presence of DIEA in an appropriate solvent followed by TFA deprotection.

## Example 110

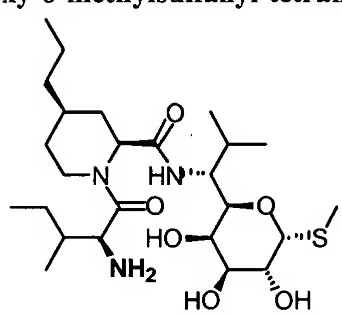
**Preparation of 1-(2-Amino-3-phenyl-propionyl)-4-propyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



[0717] The title compound may be prepared employing the method described by Weiss et al, Antimicrobial Agents and Chemotherapy, **1999**, 43 (3), 460–464, by treatment of **1** (wherein $R^1$=$R^2$=Me, $R^3$=H, $R^6$=H, $R^9$=4-cis-n-propyl, and m=2) with Boc-phenylalanine and HATU in the presence of DIEA in an appropriate solvent followed by TFA deprotection.

## Example 111

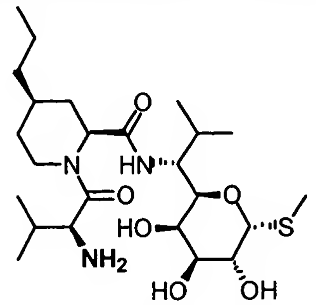
**Preparation of 1-(2-Amino-3-methyl-pentanoyl)-4-propyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



[0718] The title compound may be prepared employing the method described by Weiss et al, Antimicrobial Agents and Chemotherapy, **1999**, 43 (3), 460–464, by treatment of **1** (wherein $R^1$=$R^2$=Me, $R^3$=H, $R^6$=H, $R^9$=4-cis-n-propyl, and m=2) with Boc-isoleucine and HATU in the presence of DIEA in an appropriate solvent followed by TFA deprotection.

## Example 112

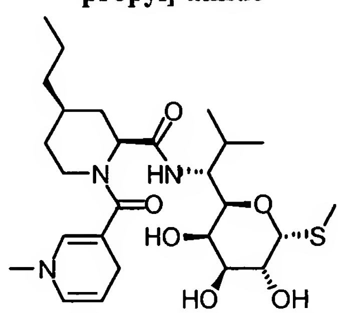
**Preparation of 1-(2-Amino-3-methyl-butyryl)-4-propyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



[0719] The title compound may be prepared employing the method described by Weiss et al, Antimicrobial Agents and Chemotherapy, **1999**, 43 (3), 460–464, by treatment of **1** (wherein $R^1$=$R^2$=Me, $R^3$=H, $R^6$=H, $R^9$=4-cis-n-propyl, and m=2) with with Boc-valine and HATU in the presence of DIEA in an appropriate solvent followed by TFA deprotection.

## Example 113

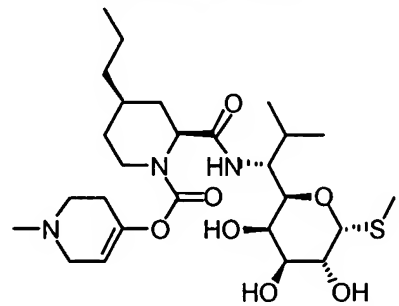
**Preparation of 1-(1-Methyl-1,4-dihydro-pyridine-3-carbonyl)-4-propyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



[0720] The title compound may be prepared from **1** (wherein $R^1$=$R^2$=Me, $R^3$=H, $R^6$=H, $R^9$=4-cis-n-propyl, and m=2) employing the method described by Shek et al, Journal of Medicinal Chemistry **1976**, 19 (1), 108–112.

## Example 114

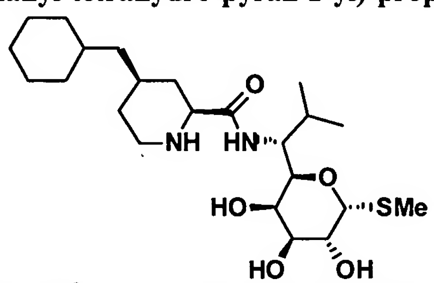
### Preparation of 2-[2-Methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propylcarbamoyl]-4-propyl-piperidine-1-carboxylic acid 1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl ester



[0721] The title compound may be prepared from **1** (wherein $R^1$=$R^2$=Me, $R^3$=H, $R^6$=H, $R^9$=4-cis-n-propyl, and m=2) employing the method described by Flaherty et al, Journal of Medicinal Chemistry **1996**, 39, 4756–4761.

## Example 115

### 4-Cyclohexylmethyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide



[0722] The intermediate **10b**, ($R^9$=benzyl) was made by employing method P using 4-benzylpyridine as the starting material.

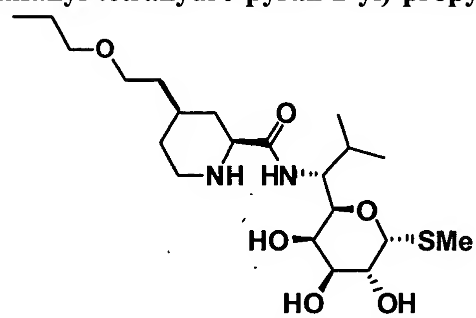
[0723] $^1$H NMR (300 MHz, $CD_3OD$) δ 8.78 (m, 1), 8.40 (s, 1), 8.03 (m, 1), 7.26-7.40 (m, 5), 4.39 (s, 2); MS (ESNEG): 212 $[M - 1]^-$.

[0724] Lincosamine **2b** ($R^1$=Me, $R^2$=Me) was coupled to 4-Benzylpyridine-2-carboxylic acid **10b** ($R^9$=4-benzyl) as depicted in general coupling scheme 11 to provide intermediate **11b** ($R^1$=Me, $R^2$=Me, $R^3$=H, $R^9$=benzyl, $P^1$=H), which was reduced by catalytic hydrogenation to the title compound.

[0725] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, J = 5.4, 1), 4.03-4.19 (m, 4), 3.78 (m, 1), 3.48-3.52 (m, 2), 3.21-3.24 (m, 2), 2.77 (t, J = 12.6, 1), 2.17 (m, 2), 2.15 (s, 3), 1.98-2.02 (m 1), 1.70-1.74 (m, 60), 1.12-1.37 (m, 8), 0.91 (d, J = 6.9, 6); MS [ESPOS]: 459 [M + H]+.

## Example 116

**4-(2-Propyloxyethyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



[0726] To a solution of 4-(2-hydroxyethyl)-pyridine (2.15 g, 17.48 mmol, 1 equiv) in glacial acetic acid (11.7 mL) was added 30 % hydrogen peroxide (1.98 mL, 17.48 mmol, 1 equiv). The reaction mixture was refluxed overnight and concentrated. The residue was dissolved in DCM, and dried (MgSO4). Solvent was evaporated under vacuum and then again co-evaporated with toluene to give the N-oxide intermediate as a syrup.

[0727] A solution of the above syrup in DCM (17 mL) was added to trimethylsilyl cyanide (2.95 mL, 22.14, 1.27 equiv) at r.t. and then cooled to 0 °C. To the mixture was added dropwise a solution of dimethylcarbamyl chloride in DCM (4.4 mL) over 10 min. The reaction mixture was stirred at r.t. overnight. A solution of 10% aqueous potassium carbonate (17.5 mL) was added dropwise and the mixture was stirred for 10 min. The organic layer was separated and the aqueous layer was extracted with DCM (2x). The combined organic layers were dried and concentrated. The residue was purified by chromatography to give the nitrile intermediate **10a** ($R^9$=2-hydroxyethyl) (0.82 g, 25 %) as a yellow oil.

[0728] $^1$H NMR (300 MHz, CDCl3) δ 8.61 (d, J = 5.1, 1), 7.56 (d, J = 0.6, 1), 7.39-7.34 (m, 1), 4.31 (t, J = 6.5, 2), 2.99(t, J = 6.3, 2), 2.02 (s, 3).

[0729] A solution of above nitrile **10a** ($R^9$=2-hydroxyethyl) (0.82 g, 4.32 mmol) in 6 N HCl (2 mL) was refluxed overnight. The reaction mixture was concentrated under vacuum. MeOH (18 mL) and water (18 mL) were added, followed by conc. aq. HCl (2.2 mL) and platinum oxide (450 mg). The mixture was purged and charged with hydrogen (1 atm) and stirred overnight.

The platinum oxide was removed by filtration and the filtrate evaporated under vacuum to afford the intermediate pipecolic acid intermediate.

[0730] The above pipecolic acid intermediate was taken in 2N NaOH (5 mL) and t-butanol (5 mL), and di-t-butyl dicarbonate (1.33 g, 6.1 mmol) was added with stirring. The mixture was stirred at r.t. overnight. The solvent was removed under vacuum. The residue was diluted with water and organic layer washed with ether. The aqueous layer was acidified with 2N HCl to pH = 2.0, and extracted with ethyl acetate (twice). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The crude N-Boc pipecolinic acid intermediate was purified by chromatography to give 4-(2-hydroxyethyl)-piperidine-1,2-carboxylic acid-1-tert-butyl ester (210 mg, 18 %) as a clear syrup.

[0731] $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.45-4.38 (m, 1H), 3.64 (t, J = 7.1, 2), 3.63-3.56 (m, 1), 3.34-3.24 (m, 1), 1.99-1.94 (m, 2), 1.85-1.65 (m, 2), 1.62-1.53 (m, 2), 1.48-1.43 (m, 1), 1.42 (s, 9).

[0732] Sodium hydride (60% in oil, 28.9 mg, 0.72 mmol, 2 equiv) was washed with hexane (2x), and dried under high vacuum. A solution of 4-(2-hydroxyethyl)-piperidine-1,2-carboxylic acid-1-tert-butyl ester (98.6 mg, 0.36, 1 equiv) in DMF (0.8 mL) was added to a mixture of the sodium hydride in DMF (0.7 mL) at 0 °C. The mixture was stirred at 0°C for 5 min, and then at r.t. for 20 min. 1-Bromopropane (0.33 mL, 3.6 mmol, 10 equiv) was added and the mixture stirred at r.t. for 3h and then quenched with water. The mixture was diluted with ethyl acetate, washed with water (1x), brine (1x), dried and concentrated to give a clear oil, which was purified by chromatography to give the ether intermediate 4-(2-propyloxyethyl)-piperidine-1,2-carboxylic acid-1-tert-butyl ester-2-propyl ester (35.8 mg, 28 %).

[0733] $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.36-4.29 (m, 1), 4.05 (t, J = 6.8, 2), 3.65-3.53 (m, 1), 3.39 (t, J = 6.5, 2), 3.32 (t, J = 6.8, 2), 3.33-3.25 (m, 1), 2.03-1.92 (m, 1), 1.87-1.70 (m, 3), 1.68-1.48 (m, 6), 1.41 (s, 9), 1.41-1.34 (m, 1), 0.97-0.84 (m, 6); MS (ESPOS): 258.2 $[M - Boc + H]^+$.

[0734] To a solution of ether intermediate 4-(2-propyloxyethyl)-piperidine-1,2-carboxylic acid-1-tert-butyl ester-2-propyl ester (73 mg, 0.20 mmol, 1 equiv) in dioxane (1 mL) and water (0.8 mL) was added lithium hydroxide monohydrate (84 mg, 2 mmol, 10 equiv). The reaction mixture was stirred at r.t. overnight. The solvent was removed under vacuum. The residue was diluted with water, washed with ether. The aqueous layer was taken up in ethyl acetate, and partitioned with 10% citric acid. The organic layer was washed with water (1 x), brine (1 x), dried and concentrated to give the acid intermediate 4-(2-propyloxyethyl)-piperidine-1,2-carboxylic acid-1-tert-butyl ester (61.1 mg, 97%) as a syrup.

[0735] $^1$H NMR (300 MHz, $CDCl_3$ ) δ 4.37-4.30 (m, 1), 3.61-3.50 (m, 1), 3.42 (t, J = 6.5, 2), 3.34 (t, J = 6.8, 2), 3.42-3.35 (m, 1), 2.06-1.95 (m,1), 1.88-1.70 (m, 3), 1.65-1.50 (m, 4), 1.43 (s, 9), 1.42-1.34 (m, 1), 0.88 (t, J = 7.5, 3).

[0736] A mixture of lincosamine **2b** hydrochloride ($R^1 = R^2$ = Me; 55.8 mg, 0.19 mmol, 1 equiv) and DIEA (50 mg, 0.39 mmol, 2 equiv) in DMF (1 mL), was added to above acid intermediate (61.1 mg, 0.19 mmol,1 equiv), followed by the addition of HBTU (80 mg, 0.21 mmol, 1.1 equiv). The reaction mixture was stirred at r.t. for 3 h. The reaction mixture was evaporated under high vacuum to dryness. The residue was diluted with ethyl acetate, washed with 1:1 10% citric acid/brine (1x), sat. aqueous sodium bicarbonate (1x), brine (1x), dried and concentrated. The residue was purified by chromatography to give the N-Boc lincosamide intermediate (60 mg, 56 %).

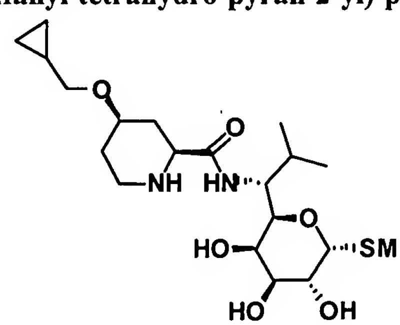
[0737] MS (ESPOS): 549.5$[M + H]^+$. MS (ESNEG): 547.2 $[M - H]^-$.

[0738] To a solution of above N-Boc intermediate in DCM (9 mL) with methyl sulfide (0.2 mL) were added trifluoroacetic acid (3 mL) and water (0.2 mL). The reaction mixture was stirred at r.t. for 1 h. The solvent was removed under vacuum and co-evaporated with toluene twice. The residue was purified by chromatography to provide the final product (lower Rf isomer, 12 mg, 25%) as a white solid.

[0739] $^1$H NMR (300 MHz, $CD_3OD$) δ 5.24 (d, J = 5.7, 1), 4.20 (dd, J = 3.3, 9.9, 1), 4.11-4.04 (m, 2), 3.83-3.76 (m, 2), 3.55-3.48 (m, 3), 3.45-3.37 (m, 1), 3.38 (t, J = 6.6, 2), 3.07-2.94 (m, 1), 2.29-2.12 (m, 2), 2.11 (s, 3), 1.98-1.83 (m, 2), 1.65-1.51 (m, 4), 1.45-1.33 (m, 2), 0.96-0.86 (m, 9); MS (ESPOS): 449.4 $[M + H]^+$; MS (ESNEG): 447.2 $[M - H]^-$.

## Example 117

### 4-Cyclopropylmethoxy-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide



[0740] The title compound was made using the synthetic sequence found in method S starting from 4-hydroxypyridine-2-carboxylic acid, substituting cyclopropylmethylbromide as the alkylating agent.

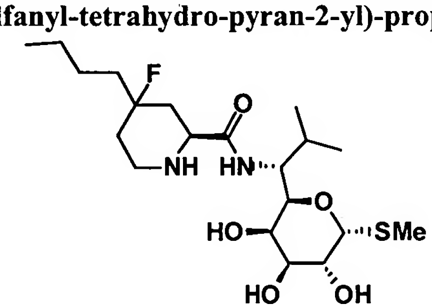
[0741] Compound **15a** ($R^{9'}$=cyclopropylmethyl): $^{1}H$ NMR (300 MHz, $CD_3OD$) δ 8.41 (d, J=4.8, 1), 7.65 (d, J=2.4, 1), 7.20 (m, 1), 4.09 (d, J=6.9, 2), 1.32 (m, 1), 0.66 (m, 2), 0.43 (m, 2); MS (ESNEG): 192 $[M - H]^-$.

[0742] Compound **15b** ($R^1$=Me, $R^2$=Me, $R^3$=H, $R^{9'}$=cyclopropylmethyl): $^{1}H$ NMR (300 MHz, $CD_3OD$) δ 8.41 (d, J=5.7, 1), 7.61 (d, J=2.7, 1), 7.07 (dd, J=2.7, 5.7, 1), 5.27 (d, J=5.4, 1), 4.87 (m, 2), 4.12 (dd, J=3.0, 10.2, 1), 3.98 (d, J=6.9, 1), 3.84 (d, J=3.0, 1), 3.56 (dd, J=3.3, 9.6, 1), 3.33 (m, 1), 2.85 (m, 1), 2.25 (m, 1), 2.11 (s, 3), 1.29 (m, 1), 0.98 (t, J=5.7, 6), 0.66 (m, 2), 0.39 (m, 2); MS (ESPOS): 427 $[M + H]^+$.

[0743] Title compound (38 mg, 18%): $^{1}H$ NMR (300 MHz, $CD_3OD$) δ 5.24 (d, J=5.4, 1), 4.88 (dd, J=6.3, 9.6, 1), 4.04 (m, 2), 4.21 (d, J=2.7, 1), 3.50 (m, 3), 3.33 (m, 2), 2.78 (m, 1), 2.30 (m, 1), 2.16 (m, 1), 2.10 (s, 3) 1.38 (m, 2), 1.02 (m, 9), 0.53 (m, 2), 0.22 (m, 2); MS (ESPOS): 433 $[M + H]^+$.

## Example 118

### 4-Fluoro-4-butyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide




[0744] The title compound was made using the synthetic sequence found in method Y (general scheme 21) starting from 4-oxo-piperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester **21a** (m=2, P=H, $P_2$=Boc), substituting butyl lithium as the $R^9$ carbon nucleophile.

[0745] Lincosamine **2b** ($R^1$=Me, $R^2$=Me) was coupled to carbamate **21d** ($P_2$=Boc, m=2, $R^9$ = n-butyl) as depicted in general coupling scheme 11 to provide intermediate **11a** ($R^1$=Me, $R^2$=Me, $R^3$=H, $R^9$=butyl/fluoro, $P^1$=H, $P^2$=carboxylic acid-t-butyl ester, m=2) which was deprotected under acidic conditions to provide the title compound.

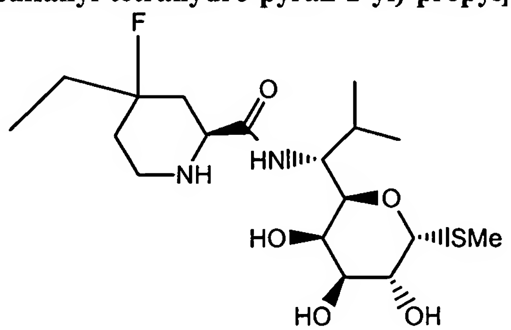
[0746] MS (ESPOS): 437 $[M + H]^+$.

## Examples 119-122

[0747] Examples 119-124 are prepared in an analogous manner as in Example 118 (Method Y, scheme 21), substituting the appropriate $R^9$ carbon nucleophile.

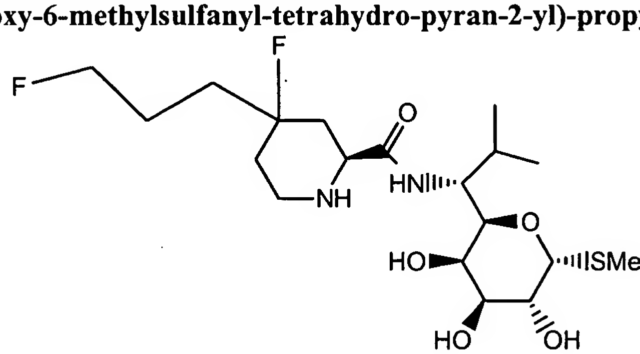
### Example 119

**4-Fluoro-4-ethyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



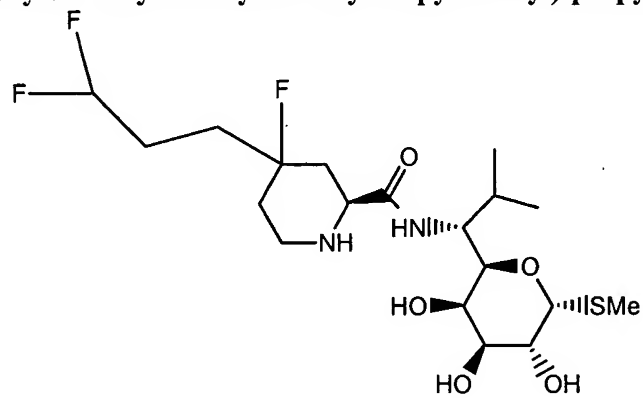

### Example 120

**4-Fluoro-4-(3-fluoropropyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



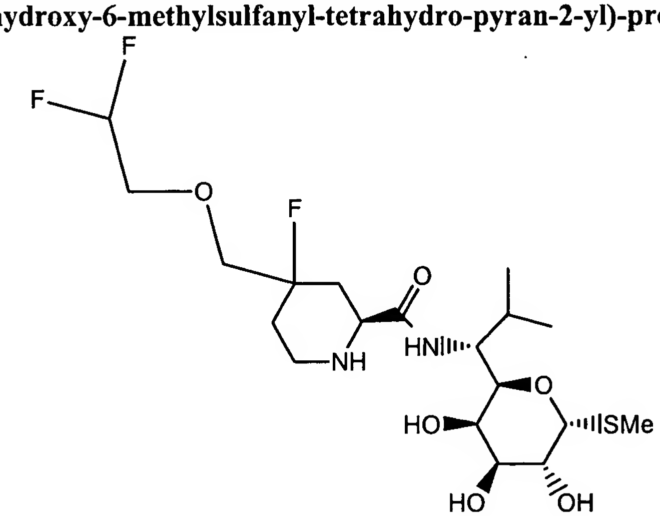
**Example 121**

**4-Fluoro-4-(3,3-difluoropropyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



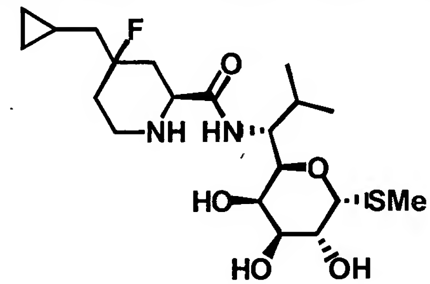
**Example 122**

**4-Fluoro-4-(2,2-difluoroethoxymethyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



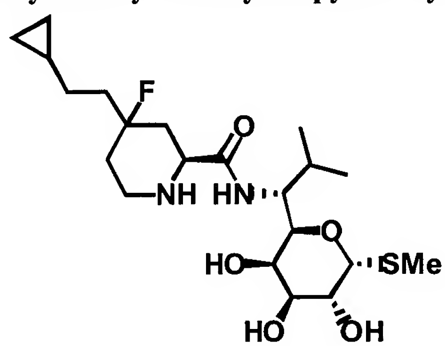
## Example 123

**4-Fluoro-4-(cyclopropylmethyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



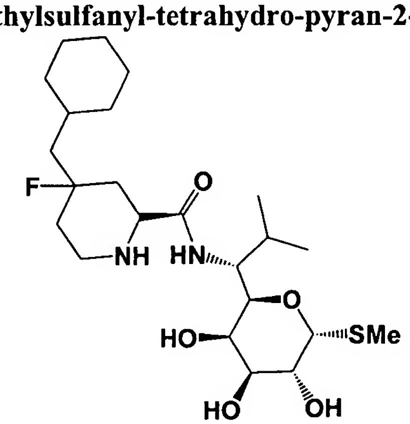
## Example 124

**4-Fluoro-4-(2-cyclopropyl-ethyl)-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



## Example 125

**4-Fluoro-4-cyclohexylmethyl-piperidine-2-carboxylic acid [2-methyl-1-(3,4,5-trihydroxy-6-methylsulfanyl-tetrahydro-pyran-2-yl)-propyl]-amide**



[0748] The following Examples may be used to test compounds of this invention.

## Example A

## Susceptibility Testing

[0749] Compounds were tested following the microdilution method of NCCLS (National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; Approved standard - fifth edition. NCCLS document M7-A5, NCCLS, Wayne, PA. 2000; National Committee for Clinical Laboratory Standards. Methods for antimicrobial susceptibility testing of anaerobic bacteria; Approved standard - fifth edition. NCCLS document M11-A4, NCCLS, Wayne, PA. 2001). Assays were performed in sterile plastic 96-well microtiter trays with round bottom wells (Greiner).

Compound Preparation

[0750] Stock solutions of test compounds and control antibiotics are prepared at 10mg/mL in DMSO. Serial 2-fold dilutions of each drug are performed in a microtiter plate across each row using DMSO as solvent at 100- fold the desired final concentration. Wells in columns #1-11 contain drug and column #12 was kept as a growth control for the organism with no drug. Each well in the mother plate is diluted with sterile deionized water, mixed, and volumes of 10 µL distributed to each well in the resulting assay plates.

Preparation of Inoculum

[0751] Stock cultures were prepared using the Microbank™ method (Pro-Lab Diagnostics) and stored at -80°C. To propagate aerobic strains, one bead was removed from the frozen vial and aseptically streaked onto Trypticase Soy Agar (Difco), Chocolate Agar (Remel) or Blood Agar (Remel) which were incubated at 35°C overnight. Anaerobes were cultivated in Brucella Agar (Remel) supplemented with hemin and vitamin K and incubated in anaerobiosis using an Anaerobic Jar (Mitsubishi) at 35°C for 24 to 48 h. Standardized inocula were prepared using the direct colony suspension method according to NCCLS guidelines (National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; Approved standard - fifth edition. NCCLS document M7-A5, NCCLS, Wayne, PA. 2000; National Committee for Clinical Laboratory Standards. Methods for antimicrobial susceptibility testing of anaerobic bacteria; Approved standard - fifth edition.

NCCLS document M11-A4, NCCLS, Wayne, PA. 2001). Isolated colonies were selected from an 18-24 h agar plate and resuspended in 0.9% sterile saline to match a 0.5 McFarland turbidity standard. The suspension was used within 15 min. of preparation.

| | |
|---|---|
| *Streptococcus pneumoniae* VSPN1001 | *Streptococcus pneumoniae* ATCC 49619 |
| *Streptococcus pneumoniae* VSPN3026 | *Streptococcus pneumoniae* R6x |
| *Streptococcus pneumoniae* VSPN4054 | *Streptococcus pneumoniae* 488K |
| *Streptococcus pneumoniae* VSPN4021 | *Streptococcus pneumoniae* 9 |
| *Staphylococcus aureus* VSAU1017 | *Staphylococcus aureus* Smith |
| *Staphylococcus aureus* VSAU1003 | *Staphylococcus aureus* ATCC 25923 |
| *Staphylococcus aureus* VSAU4020 | *Staphylococcus aureus*125 |
| *Staphylococcus aureus* VSAU4048 | *Staphylococcus aureus* 85-EPI |
| *Staphylococcus aureus* VSAU4065 | *Staphylococcus aureus* VSAU4065 |
| *Staphylococcus epidermidis* VSEP1001 | *Staphylococcus epidermidis* ATCC 12228 |
| *Enterococcus faecalis* VEFL1003 | *Enterococcus faecalis* ATCC 51299 |
| *Enterococcus faecium* VEFA1005 | *Enterococcus faecium* BM4147.1 |
| *Haemophilus infuenzae* VHIN1003 | *Haemophilus infuenzae* ATCC 49766 |
| *Haemophilus infuenzae* VHIN1004 | *Haemophilus infuenzae* ATCC 31517 |
| *Haemophilus infuenzae* VHIN1005 acr | *Haemophilus infuenzae* LS-2 |
| *Moraxella catarrhalis* VMCA1001 | *Moraxella catarrhalis* ATCC 25238 |
| *Escherichia coli* VECO2096 | *Escherichia coli* MG1655 |
| *Escherichia coli* VECO2526 tolC | *Escherichia coli* MG1655 to1C |
| *Bacteroides fragilis* VBFR1001 | *Bacteroides fragilis* ATCC 25285 |
| *Bacteroides thetaiotaomicron* VBTH 1001 | *Bacteroides thetaiotaomicron* ATCC #29741 |
| *Clostridium difficile* VCDI1001 | *Clostridium difficile* ATCC 9689 |

Preparation of Assay Plates for MICs Preparation of Assay Plates for MICs

**[0752]** Media were prepared at 1.1 x concentration. Mueller-Hinton Broth MHB (Difco) supplemented with Ca++ and Mg++ as recommended by NCCLS, MHB supplemented with 5% horse lysed blood, HTM Broth (Remel), or Brucella broth (Remel) supplemented with hemin and vitamin K. For each organism, the standardized suspension was diluted into appropriate growth medium in a sterile reservoir. After mixing, wells in the drug-containing assay plates were inoculated with a volume of 90μl. Thus, for each MIC determination, each well contains a final volume of 100 μL with an inoculum size of approximately 5 * 105 cfu/mL and no more than 1% DMSO.

Interpretation of MIC

**[0753]** The completed microtiter plates were incubated 16-20 h at 35°C in ambient air for aerobes, and at 35 °C for 46-48 h or in an anaerobe jar (Mitsubishi) for anaerobes. Optical density of each well was determined at 600 nm using a VersaMax Microplate reader (Molecular Devices, Sunnyvale, CA). The MIC was defined as the lowest drug concentration causing complete suppression of visible bacterial growth.

## Example B

## Efficacy in Murine S. aureus Septicemia

**[0754]** Efficacy studies were performed in an S. aureus murine septicemia model according to models published elsewhere (Goldstein, B. P., G. Candiani, T. M. Arain, G. Romano, I. Ciciliato, M. Berti, M. Abbondi, R. Scotti, M. Mainini, F. Ripamonti, and et al. 1995. Antimicrobial activity of MDL 63,246, a new semisynthetic glycopeptide antibiotic Antimicrob Agents Chemother. 39:1580-1588.; Misiek, M., T. A. Pursiano, F. Leitner, and K. E. Price 1973. Microbiological properties of a new cephalosporin, BL-S 339: 7-(phenylacetimidoyl-aminoacetamido)-3-(2-methyl-1,3,4-thiadiazol-5-ylthio methyl)ceph-3-em-4-carboxylic acid Antimicrob Agents Chemother. 3:40-48).

Compound Preparation

**[0755]** Compounds were dissolved in 2% Tween 80 for oral dosing or 0.9% NaCl solution for intravenous dosing. Compounds were administered at 1 hour after bacterial inoculation. Vancomycin or ampicillin were used as controls.

Efficacy model

**[0756]** Male or female ICR mice weighing 22±2 g from MDS Pharma Services were used for the evaluation. Food and water was given ad libitum. Groups of 6 mice weighing 22 ± g were used for the experiment. Mice were inoculated intraperitoneally with Staphylococcus aureus Smith at 4 104 CFU in 0.5 mL of Brain Heart Infusion Broth (Difco) containing 5% mucin (Sigma). Mortality was recorded once daily for 7 days following bacterial inoculation.

**[0757]** While the invention has been described and illustrated herein by references to various specific material, procedures and examples, it is understood that the invention is not restricted to the particular material combinations of material, and procedures selected for that purpose.

Numerous variations of such details can be implied as will be appreciated by those skilled in the art.

## Example C

### In vivo animal model

[0758] In vivo activity of various compounds of the subject invention was evaluated in a standard Staphylococcus aureus septicemia model (MDS Pharma Services, Bothell, WA).

[0759] Male ICR-derived mice (ICR is a strain of out-bred mice) provided by MDS Pharma Services animal breeding center were inoculated intraperitonealy with $LD_{90-100}$ of Staphylococcus aureus (Smith; ATCC19636) in 0.5mL BHI broth containing 5% mucin (Sigma). Compounds were formulated in 2% Tween 80 (Sigma) and single doses were administered orally one hour after bacterial inoculation. Mortality was monitored daily for seven days.

[0760] In previous studies, the oral $ED_{50}$ (i.e., concentration that protected 50% of the mice) was determined to be 19.9 mg/kg for clindamycin, a commercially available lincosamide (Sigma). To screen the compounds of this invention that were tested, compounds were administered at 10 mg/kg to a group of eight ICR mice and the number of survivors at that concentration was compared to clindamycin. Results are presented in the table below.

| **Compound Tested (Indicated by Example No.)** | **No. of surviving mice at 10 mg/kg** |
|---|---|
| Clindamycin | 6 |
| 17 | 1 |
| 34 | 2 |
| 35 | 2 |
| 36 | 0 |
| 100 | 7 |
| 101 | 7 |

It is assumed that when compound from example 36 is tested at a higher dose, the number of surviving mice would increase.